ANTIGEN PRESENTATION

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ABSTRACT

Antigen presentation is a critical step in the initiation of immune response. Many types of cells can serve this function but the macrophages are the principal cells. The antigen-presenting cells (APC) must express Ia antigens and most of them produce interleukin-1. Macrophages bind, endocytose, catabolize and then express the antigen on the surface in the context of Ia and present it to T and B lymphocytes. On the other hand, B-lymphocytes present the native antigen (without catabolism) in the context of Ia antigen to helper T cells. The nature of APC, their functions and factors modulating them have been discussed.

THE most crucial step in the initiation of the immune response is the presentation of antigen in proper immunogenic form, in appropriate dose, to the appropriate cell. The function of antigen presentation is carried out by a special class of bone marrow-derived, mostly of nonlymphoid, cells which probably belong to the mononuclear phagocyte series. The antigen presenting cells (APC), except for the macrophages (Mϕ) are usually nonphagocytic and do not have a full complement of lysosomal enzymes. But they always express large amounts of Class II major histocompatibility complex (MHC) Ia antigen and function in MHC-restricted fashion. The APC include Mϕ in the peritoneal cavity and tissues, dendritic or interdigitating cells in spleen and lymph nodes, Langerhans cells in the epidermis, the veiled cells in the afferent lymph and Peyers patches and the B lymphocytes in spleen and lymph nodes. Besides these classical APC, antigen can also be presented by T cells[1] and epithelial cells[2] under certain circumstances. Some of the features of these cells are summarized in table 1.

ANTIGEN-PRESENTING CELLS

Origin and differentiation of APC:

Monocytes are the precursors of Mϕ[3] and it appears that a subset differentiates into the nonphagocytic dendritic cells. Precursor cells derived from the central pool in bone marrow, leaving the blood stream in the papillary layer of the dermis, enter the epidermis to become Langerhans cells[4]. Some of these cells return to the dermis and enter the afferent lymphatics to become veiled cells[5]. These cells enter the marginal sinus of the lymph node and finally reach the T-dependent area in paracortex and gradually change into mature interdigitating cells.

Macrophages

The most important cells responsible for the presentation of antigen to T and B lymphocytes are the macrophages which express Ia antigens. These cells are fairly large with varying amounts of cytoplasm and have a reniform or oval nucleus. Cytoplasmic organelles for secretory activities are abundant in more mature form of the tissue Mϕ[6]. The functional properties shared by cells of the mononuclear phagocyte system are avid phagocytosis, pinocytosis and the ability to adhere firmly to glass or plastic surface[6]. Mϕ are highly secretory cells and therefore, can exert a considerable influence on their extracellular environment[7]. The secretory function is very important in intracellular handling of microbes and other foreign material. The major stimulus

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Table 1 *Some characteristics of antigen presenting cells*

Cells	Phagocytosis	Ia antigen	Receptors: Fc	Receptors: C3	Enzymes: Acid phosphatase	Enzymes: Esterase	Enzymes: ATPase
Macrophages	+	+	+	+	+	+	+
Dendritic cells	−	+	−	−	−	−	+
Langerhans cells	±*	+	+	+	+	+	+
Veiled cells	−	+	+	+	±	±	+
B-lymphocytes	±	+	+	+	−	−	−

*± weakly or may be positive.

for secretion is the process of phagocytosis of particles.

One major function of the Mϕ is the uptake of antigens, degradation and the presentation of these molecules to the lymphocytes in a form that is immunogenic. Mϕ are the necessary accessory cells for activation of lymphocytes *in vitro*. This Mϕ requirement has been demonstrated for T-lymphocyte activation by antigens[8], mitogens and allogeneic cells[9–11]. They are required for antigen-specific activation of mediator production by T-lymphocytes because recognition of soluble protein antigen by the T-lymphocyte is actually preceded by an initial uptake of antigen by the Mϕ[12]. The Mϕ are also required for development of antibody forming cell (PFC) responses in all immunoglobulin classes to both T-cell dependent and T-cell independent antigens[13].

Dendritic cells

These are large cells with long processes and an irregular horseshoe-shaped nucleus with heavy chromatin accumulation on the nuclear membrane and one or two nucleoli. The cytoplasm is fairly electronlucent having some polyribosomes, many mitochondria and very little RER. The golgi apparatus is well developed. There are many small vesicles but very few of them contain lysosomal granules or phagolysosomes.

Dendritic cells are temporarily adherent, highly Ia-positive, nonphagocytic and Fc receptor negative cells but exhibit a highly effective antigen presentation function[14,15]. These cells stimulate allogenic and autologous mixed lymphocyte reaction (MLR), assist in the generation of cytotoxic T-lymphocytes and increase the proliferative response of lymphocytes by stimulation with mitogen or antigen. They act mainly on T-lymphocytes, probably by releasing interleukin-I and also antigenic fragments complexed with Ia antigen, but may also have a role in B-cell triggering.

Langerhans cells

Langerhans cells are found in most squamous epithelia including the skin, buccal mucosa, oesophagus and vaginal and rectal mucosa of mammals. Langerhans cells have many dendrites, electron dense cytoplasm and numerous Birbeck granules. They have Fc and C3 receptors, bear histocompatibility antigen of the D/DR and I-A and I-E/C regions[16]. Langerhans cells are weakly phagocytic and contain lysosome-like bodies and acid phosphatase. Langerhans or Langerhans-like cells are also found in the dermis and in lymphoid organs including thymus, lymph nodes and spleen and may resemble abnormal macrophage-like cells[17].

Langerhans cells are an important component of the immune system and can present

antigen, control lymphocyte cell traffic, and may play a role in the intrathymic conditioning and differentiation of T-lymphocytes. An antigen presented by Langerhans cells induce contact hypersensitivity, but in the absence of these cells immunological tolerance develops[18]. Langerhans cells can replace other APC such as Mϕ in specific activation of T-lymphocytes. Syngenic Langerhans cells sensitized with ovalbumin, PPD or TNP can induce proliferation of lymphocytes but they fail to stimulate in allogenic conditions and lose activity after treatment with anti-Ia serum and complement. Human Langerhans cells have been shown to present PPD[19] herpes simplex virus[20] and nickel[21] antigens.

Veiled cells

These are large cells with veil-like processes and are found in mesentric and skin lymph. They express class I and class II MHC antigens and a small proportion have surface immunoglobulin[22]. Veiled cells do not divide in culture, do not have Fc-receptors and some of them have C3 receptors. They are glass nonadherent, are extremely active, extruding large boat-shaped veils. In the skin, these cells have many characteristics of dendritic and Langerhans cells. Both have Fc and C3 receptors and a large amount of ATPase in the cell membrane[23]. But these properties are lost when the cells enter the lymph node and acquire the ability to stick to glass surface. They stimulate and increase the lymphocyte reaction and responses of lymphocytes to stimulation by mitogens. They provide the signal for allograft rejection.

B-lymphocytes

B cells have the capacity to present antigen efficiently like macrophages. The antigen is bound to the immunoglobulin present on the surface of B cells and internalized in a vesicle containing Ia molecules. The surface immunoglobulin is partly degraded in the vesicle and is not re-expressed in native form[24], but Ia molecule-antigen complex is re-expressed on the surface and presented to macrophages or to T-helper cells[25,26]

EXPRESSION OF Ia ANTIGEN

The MHC class II glycoproteins (Ia antigen) are found on Mϕ and other APC as shown in table 1. The activation of T helper cells is induced only by antigen presented by an APC that displays the Ia antigen and not by free antigen[27]. The expression of Ia antigen on Mϕ is transient, is independent of mature T lymphocytes or the presence of antigen[28,29] and develops mainly in young Mϕ. The basal level of Ia positive Mϕ in an organ is maintained by continuous differentiation of stem cells to Mϕ and conversion of Ia positive into Ia negative cells (if it is true). The regulation of expression of Ia molecules on APC can be a critical step in the control of immune response. The amount of Ia molecules on APC can be correlated with the capacity to present antigen for the development of helper T cells (reviewed in 31). The antigen-presentation can be blocked by pretreatment of Mϕ with anti-Ia antibodies (reviewed in 30). The processes which modulate Ia expression may therefore influence the immune response significantly.

The expression of Ia on Mϕ can be enhanced by (i) phagocytosis triggering agents which maintain Ia expression and check the change of Ia positive to Ia negative[29] (ii) lymphokines, (specially gamma interferon), preferentially induce Ia expression on previously immature Ia negative macrophages[32–35] and (iii) *in vivo* injection of live bacteria e.g. *Listeria monocytogenes*[36] and bacterial lipopolysaccharide (LPS)[37]. On the other hand a number of inhibitory molecules diminish Ia expression viz (i) prostaglandin E[38,39] (ii) α-fetoprotein[31] (iii) corticosteroids[39] and (iv) *in vitro* inoculation of LPS[34]. (v) Further, the number of Mϕ which expresses Ia antigen is reduced by irradiation[33] and (vi) in lactic dehydrogenase elevating virus infection[40]. Thus, Ia expression is regulated by positive and negative external stimuli and may ultimately influence the anti-

gen presentation and the consequent immune response. This could be, due either to impairment of the expression of Ia molecules on the membrane or due to the elimination of Ia positive cells.

PRODUCTION OF INTERLEUKIN-1 (IL-I) BY APC

Mϕ exert regulatory influence at various stages in the life of the lymphocytes. A low molecular weight, antigen-nonspecific peptide termed as interleukin-1 (IL-1) produced by most Mϕ appears to act as a maturational signal or secondary mediator signal for preparing T-cells to respond to antigens[41,42]. A novel form of IL-1 bound to plasma membranes of APC[43] and B lymphocytes[44] has been described recently. T-cell clones have been shown to respond to antigen presentation only when both Ia and IL-1 are expressed and the response depends upon the amount of each[44]. One of the major activities of IL-1 is to induce the synthesis and secretion of the T cell derived mitogenic lymphokine, Interleukin-2 (IL-2)[42, 45,46]. This link between IL-1 and IL-2 is an essential element in the T cell activation sequence as it involves the conversion of a priming Mϕ derived maturational signal into a secondary T cell derived proliferative signal which results in the amplification of specific immune response. Among APC, IL-1 is also produced by dendritic cells[47], Langerhans cells[48] and B lymphoblasts[49].

ANTIGEN PRESENTATION BY Mϕ

The process of antigen presentation includes binding, endocytosis, active catabolism of the antigen followed by reaching the surface of Mϕ and presentation to T or B lymphocytes. The predominant functions of different APC are summarized in table 2. The antigen may bind non-specifically at any area of the plasma membrane of Mϕ by non-covalent interaction or by specific receptors viz. Fc, C3, Ig or the virus receptors. Bindings through receptors is very efficient as compared to non-specific binding which depends on the concentration of

Table 2 *Predominant functions of antigen presenting cells*

Cells	Functions
Macrophages	Generation of T-helper cells.
Dendritic cells	Powerful stimulants of syngeneic and allogeneic interactions react with selected antigens that require minimal processing.
Langerhans cells	Sensitization to skin-bound antigens.
Veiled cells	Allograft rejection.
B-lymphocytes	Interaction with T-helper cells.

the antigen[50]. Further, Mϕ can take up two different antigens added simultaneously or in sequence[51].

The endocytosed antigen is actively catabolized and most of the proteins are degraded to amino acids or the molecules are unfolded by the action of lysosomal proteases[52]. Antigen processing through active metabolism takes about one hour to complete and can be blocked by treatment of Mϕ with lysosomotropic agents, ammonium chloride or chloroquine[44, 50, 53]. For the processing of antigen it is essential that Mϕ are live, but once the recycled antigen has reached the cell membrane, fixation of Mϕ does not affect antigen presentation[44, 52]. The small peptides incorporated on the cell membrane have a short life and are displayed in such a way as to be recognized by the T-cells[31] Some antigenic components can be released from Mϕ as soluble products. The random contact between membrane bound antigen and Ia may result in an association, the affinity of which is dictated by the structure of both proteins[27]. Only a minority of macrophages can present antigen to T-cells[7]; these cells must possess easily demonstrable Ia antigens. Part of the processing step, therefore, appears to be the association of antigens moieties with Ia surface molecules. Recognition of Mϕ associated antigen by T-lymphocytes requires cell contact; strong immunogenicity of macrophage associated antigen is found with all kinds of antigen whether particulate or soluble, large or small proteins[54]. Recently four routes of processing

of the influenza virus antigens have been suggested, namely (i) the classical lysosomal route, (ii) the dissociation of the contents of the endosomes without entry in lysosome, (iii) the excretion of newly synthesized viral glycoproteins by the Golgi apparatus and expression on cell surface, and (iv) the processing of virus antigen at cell membrane (reviewed in 55). Thus, the alternate route of antigen processing allows recognition of tertiary structures without involving endocytosis and proteolytic digestion.

The need for antigen processing may be due to the class I or class II MHC elements involved or due to the nature of the antigen. The processing of antigen to small peptides may be required to reduce the steric hindrance in class II restricted response which is not needed in class I restricted response[50]. Further, processing may not be required for those antigens which bind to the and exist as an integral part of the plasma membrane of the APC; (for example the viral glycoproteins) but is certainly needed for those antigens which do not bind to cell membrane as the soluble protein antigen. B lymphocytes bind native antigen through Ig receptors; therefore, processing of antigen is not required. Thus, processing is required to make antigen available at the surface of APC for recognition by helper T cells.

Presentation of antigen to helper T cells

Mϕ presents the antigen along with a definite Ia molecule epitope to the helper T cells by direct cell to cell contact. Different antigens can be present with different epitopes, the number of immunogenic determinants being high, and the physical association between Ia and antigen appears to be polygamous. The antigen primed helper T cells bind rapidly to the APC *in vitro* followed by the binding of other lymphocytes making a cluster which acts as a nidus for T-cell differentiation and proliferation. Following interaction with T-cells, Mϕ releases IL-1 which stimulates lymphocytes and this induces the responding T-cell subset to release IL-2 which interacts with activated antigen specific T-cell, to expand them clonally.

Presentation of antigen to B cells:

There are probably more than one pathway by which B cells activate. Helper T cells release antigen specific Ia positive T-helper factor which along with the antigen, and possibly through the accessory cells, activate and initiate the response in B cells and to some extent their clonal expansion. The differentiation signal is provided by the antigen non-specific T-cell factor such as IL-1 and IL-2 and the 40,000 molecular weight T-cell replacing factor (TRF). This non-specific signal may be produced by a class of T-cells different from those presenting the antigen-specific signal[56,57].

ANTIGEN PRESENTATION BY OTHER APC

The marginal zone macrophages and the follicular dendritic cells of spleen and lymphnodes remain in close contact with lymphocytes and do not express Ia antigen. They retain antigen on their surface for a long period of time and may be a persistent source of antigen for B lymphocytes which do not need Ia molecules for recognition of antigen. B lymphocytes are, themselves, capable of presenting soluble protein antigens to primed helper T cells in an antigen-specific and MHC-restricted manner and may result in focussing the antigen-specific helper T cells to the surface of antigen-specific B cells[50,58–60]. There are a number of other cell types which have Ia molecules and may have the capacity to present antigens viz skin keratinocytes[61], epithelial cells the 'nurse cells' of thymus[62], veiled and interdigitating cells in skin and lymphnodes[22,63] and mitogen or allo-antigen stimulated T cells[64,65] but the latter may deliver 'tolerogenic' signal[66].

MECHANISM OF ANTIGEN PRESENTATION

The exact mechanism of the presentation of the processed antigen by the APC to helper T

cells, in the context of Ia antigen is not known. Three groups of investigators have presented evidence that the processed antigen is complexed with Ia molecule, creating single macromolecular ligand, which is presented to the single receptor on the T cell[67–69]. A bimolecular complex mechanism has been suggested by Rosenthal *et al*[70] and others[71,72]. On the other hand a trimolecular model has been proposed[73] involving a complex between Ia molecules, antigen and a T cell receptor, each having a positive affinity for the other two. Similar models, with very little variations, have been proposed recently by Parham[74] and Grey & Chesnut[50], but none of the mechanisms is exclusive.

Factors affecting antigen presentation

The factors which affect the binding, uptake, catabolism and expression of antigen on the surface of APC, influence the antigen presentation. Thus, factors controlling Ia expression or IL-1, modulate the antigen presentation as discussed earlier. Treatment of Mϕ with ammonium chloride or chloroquine inhibits their capacity of catabolism and thus antigen presentation[53].The drugs effect the intracellular handling step of antigen via disruption of normal lysosomal functions by increasing lysosomal pH thus depressing the activity of acid hydrolases.

CONCLUSION

Many different types of cells have functional capacity to present antigen but which or how many of them actually take part *in vivo* is not well understood. It is likely that different sets of cells cooperate with each other in a particular situation to present antigen for an optimum immune response. APC must express Ia to present antigen, but all cells having Ia may not present it. Modulation of Ia expression on APC regulates the antigen presentation function, and thus, the immune response to an antigen. The precise mechanism of antigen processing and presentation is also not clear. An antigen may be processed by different routes by different APC, for example purified protein derivative (PPD) and keyhole limpet haemocyanin (KLH) are processed by internal lysosomal route by macrophages and by membrane bound mechanism by B lymphocytes (reviewed in 55). The processing of an antigen may depend upon (i) the nature of APC (ii) the nature of antigenic determinant and (iii) the specificity of the T cells, but what actually regulates it, is not yet known. A lot more work is needed to answer these questions for a better understanding of the phenomenon of antigen presentation.

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ANNOUNCEMENTS

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The International Congress of Plant Physiology will be held under the auspices of the Society for Plant Physiology and Biochemistry in collaboration with the Indian Society for Plant Nutrition and the International Association of Plant Physiology. The congress will be held during February 15–28, 1988.

For details please contact: Shri S. K. Sinha, Secretary General, Water Technology Centre, IARI, New Delhi 110 012.

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