

Review article

Immunopathologic effect of antigen recognition

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Intracellular and extracellular antigens differ considerably in their processing and presentation to T lymphocytes (19). Peptides derived from intracellular antigens are generally presented to CD8+ T cells by major histocompatibility complex (MHC) class I molecules, which are expressed on virtually all somatic cells, while peptides derived from extracellular antigens are presented to CD4+ T cells by MHC class II molecules normally expressed by specialized, antigen-presenting cells (APC) (8). Thus, class I molecules bind to peptides derived both from pathogens entering the cytosol and from endogenously synthesized proteins. In contrast, class II molecules usually bind peptides derived from exogenous proteins taken up by professional APCs (macrophages, dendritic cells) which internalize soluble proteins by pinocytosis or endocytosis mechanisms (25). From these observations, the concept of endogenous and exogenous pathways has been developed (9, 29).

Endogenous and exogenous processing pathways and presentation

The crystal structure solution of MHC class I molecule, HLA-A2, has revealed that the peptide-binding portion at the membrane distal phase of the molecule (6) and the peptide-binding portion of class II molecules are, as has been proposed, similar to that of class I molecules (10). The polymorphic residues

of the MHC molecule groove account for the varying ability of different forms of MHC molecules to bind a variety of peptides. However, different peptides bind the grooves of class I and class II molecules, since they have different sites. The groove of class I molecules is closed at both ends, in line with the finding that the naturally processed peptides isolated from purified class I molecules are of restricted length (8-9 amino acids) (11, 15, 47). Structural analyses of these naturally purified peptides reveal the presence of simple amino acid sequence motifs that are specific to particular allelic forms of class I molecules and that have the striking conservation of the N- and C-termini amino acids anchoring the groove of class I molecules (16, 40). In contrast, class II molecules bind slightly larger peptides (15-17 amino acids) showing heterogeneity at both N- and C-termini and containing a binding motif variably placed within the peptide chain; this suggests that the peptide-binding groove of class II molecules can be open at both ends (22).

Recognition of exogenous antigens by class II restricted CD4+ T cells requires, in most cases, their uptake by professional APCs and their processing in endosomes, where they are degraded by the acid environment, and fragmented into short peptides by proteases. The endosomal pathway intersects the biosynthetic route of class II molecules (1): newly synthesized class II molecules release invariant chains in endosomes and can thus bind peptides

generated by the processing of exogenous antigens. Consequently, the class II peptide complex may be transported on the membranes of APCs for its presentation to CD4+ T cells (9).

In contrast, endogenously synthesized antigens seem to be degraded into peptides by a distinct subset of the cellular pool of proteasomes called the low-molecular-mass polypeptides (LMP complex), whose encoding genes map to the class II region of the MHC (32). The LMP complex contains multiple catalytic sites and may produce multiple peptides simultaneously from the same protein: such catalytic sites may be situated in the complex to facilitate the preferential production of nonamers. On the other hand, recent evidence indicates that neither LMP proteins nor proteasomes are essential in the functional processing of peptides for presentation by class I molecules (2, 31).

At any rate, peptides are subsequently translocated to the endoplasmic reticulum (ER) lumen by the TAP transporters, which reside in the ER membrane and are probably composed of a heterodimer of TAP-1 and TAP-2 gene products that map to the class II region, as well as genes encoding LMPs (14, 38, 44–46). Peptides transported into the ER preferentially bind to class I molecules and not to class II molecules, whose grooves are occupied in the ER lumen by C-termini of invariant chains. Peptides binding to class I molecules take part in their stabilization, facilitating their transport to the cell surface (9).

Both proteasomes and transporters are polymorphic, and this polymorphism may result, in different persons, in the production of different sets of peptides by LMPs or in different subsets of peptides translocated by transporters into the ER. If so, we assume that different epitopes of the same antigen may be presented to T cells in different persons. This may contribute to individual differences in immune response to antigens, as well as to tolerance induction and predisposition to autoimmunity. Moreover, this polymorphism may provide new genetic linkage between these genes and MHC genes.

Exceptions to the rule of class I/class II discrimination

Recent evidence has demonstrated that endogenous antigens may also be presented to class II restricted T cells (24, 35). Endogenous antigens usually enter the endosomal compartment by a still unknown mechanism (23, 24, 35). Here they are degraded and fragmented into peptides of 15–16 amino acids, which selectively bind class II molecules. Thus, peptides from endogenous and exogenous antigens may be generated in the same compartment and be available for binding to class II MHC molecules. In ad-

dition, nonendosomal processing of endogenously synthesized antigens into peptides presented by class II molecules has been shown; this suggests two routes in the presentation of endogenous antigens to class II restricted T cells (28, 35).

In contrast, the presentation of exogenous antigens to class I restricted T cells remains a very rare exception; it has been demonstrated for only a small number of antigens (4, 5, 24, 33, 50). For example, the hemolysin of *Listeria monocytogenes*, which is a cytolytic protein, lyses the phagosomal membrane and enters the cytoplasm of host cells (37). In the same manner, the hepatitis B envelope antigen (HBenvAg) may have access to the cytoplasmic compartment by its fusion with cellular membranes (4).

However, exogenous antigens require some non-endosomal forms of processing to be presented to class I restricted CTL (4). For example, treatment of APCs, during pulsing with soluble HBenvAg, with chloroquine, which inhibits the endosomal processing pathway, blocks the antigen presentation to CD4+ T-cell clones, but not to CD8+ T-cell clones, while the APC fixation eliminates the antigen presentation to both class II- and class I-restricted T cells, suggesting that exogenous HBenvAg requires a chloroquine-insensitive form of processing, operating in an extraendosomal compartment, to be presented to class I-restricted T cells.

Consequences of the exceptions of class I/class II discrimination in immunopathology

The presentation of either exogenous antigens (in particular, soluble proteins of pathogens) to class I-restricted CTL, or endogenous antigens to class II-restricted T cells may complicate the immunopathologic process. Indeed, during infections, lysis of uninfected epithelial cells may also occur because they may process exogenous viral antigens and present their peptides to class I-restricted CTL, leading to the amplification of the immunopathologic process (3).

Furthermore, during the chronic inflammatory response, it has been demonstrated that epithelial cells may spontaneously express class II molecules, which are normally expressed only by lymphoid cells (17). Notably, in this connection, it has been established that some cytokines, such as interferon gamma (IFN- γ) and tumor-necrosis factor (TFN), may induce *in vitro* expression of class II molecules on epithelial cells normally negative for these molecules (17). In the light of this evidence, it is plausible that epithelial cells positive for class II molecules may process both exogenous and endogenous antigens and present their peptides to class II-restricted T

lymphocytes, which, if cytotoxic, may participate in the killing of both infected and uninfected host cells, with consequent further amplification of the immunopathologic process.

Role of antigen presentation in the promotion of Th1-like or Th2-like responses in man

Several lines of evidence indicate that CD4+ T cells can be categorized in the mouse into two subclasses, Th1 and Th2, by the array of cytokines they secrete (7, 30, 34). It has been found that Th1 cells produce IL-2 and IFN- γ upon activation, but not IL-4, IL-5, IL-6, and IL-10, and that Th2 cells secrete IL-4, IL-5, IL-6, and IL-10, but not IL-2 and IFN- γ . Th1 cells induce either activation of macrophages to kill intracellular parasites, or delayed hypersensitivity (DTH), or IgG2a, but not IgE, synthesis. Th2 cells promote IgG1 and IgE production by B cells, and eosinophilia.

Although most human CD4+ T-cell clones simultaneously produce all the above-mentioned cytokines (thereby resembling Th0 cells), human T-cell clones with Th1-like or Th2-like profiles have recently been described (27, 36). The selective activation of either Th1 or Th2 cells has been supposed to be determined by different factors; such as accessory cell costimulation or the nature of the antigen or peptides recognized by CD4+ T cells (13, 20, 21, 30, 41, 43, 48, 49, 51). For example, it has been shown that pathogens such as mycobacteria or *Borrelia burgdorferi* promote the Th1 response (13, 20), while allergens such as those of *Toxocara canis* promote the Th2 response (13). On the other hand, recent evidence indicates that the promotion of either the Th1 or the Th2 response is not always related to the nature of the antigen. For example, HBenvAg can induce antigen-specific CD4+ T-cell clones with either Th1-like, Th2-like, or Th0-like profiles. It is interesting to find that most HBenvAg-specific CD4+ T-cell clones with Th1-like profiles derive from the livers of patients affected by chronic active hepatitis, while those isolated from peripheral blood lymphocytes (PBL) are distributed evenly among the three different groups of Th1-, Th2-, and Th0-like cells (Barnaba, paper in preparation). The finding that the HBenvAg-specific Th1-like T-cell clones with cytotoxic activity are preferentially compartmentalized in tissues with chronic inflammatory damage is consistent with the hypothesis that the environment may influence the selective promotion of a Th response. Recently, it has been reported that the differential regulation of T-helper phenotype development is determined by the presence of different cytokines during *in vivo* or *in vitro* primings: IL-4 and

IL-10 promote the differentiation of Th precursors into Th2; IFN- γ into Th1 (39, 43). Taken together, these data suggest that a variety of mechanisms may be involved in the promotion of the Th1- or Th2-like response, including those involved in antigen presentation and T-cell priming. Thus, *in vivo* priming with pathogens within the tissue environment may facilitate the stimulation and the subsequent expansion of cytotoxic CD4+ T lymphocytes with a Th1-like profile, perhaps with the influence of the inflammatory cytokines (IFN- γ) presumably produced by cytotoxic class I-restricted T cells. In this regard, it has been proposed that IFN- γ , IFN- α , and IL-12, all strongly involved in the natural immune response to viruses (IFN- α and IL-12 produced by macrophages; IFN- γ by NK cells), promote differentiation of the Th precursor into Th1 cells (39). These CD4+ T cells, which accumulate in virus-infected tissues, can subsequently participate in inflammatory responses by direct lysis of host cells, or by delayed hypersensitivity reactions. Nevertheless, CD4+ T cells with a Th1-like profile and cytotoxic activity may also kill other T cells; the latter have been recently shown to be able to acquire antigen-presenting capacities, participating in the downregulation of T-cell responses (18, 26).

In contrast, CD4+ T cells, which have a different *in vivo* priming by soluble antigens (e.g. allergens, soluble viral antigens) presented by different APCs (perhaps in the presence of different cytokines) in peripheral lymphatic or mucosal tissues, may be promoted toward a Th0- or Th2-like response. The lack of IFN- γ , presumably determined by a defect of NK cell function, and the presence of IL-4 have been assumed to be essential for the generation of Th2 responses with the subsequent amplification of allergic reactions (39).

All the findings reported here not only solve an interesting intellectual puzzle, but also may be very important in finding new therapeutic approaches by the manipulation of Th1 and Th2 responses. For example, the ability to shift the differentiation of specific T cells from the Th2- to the Th0- or Th1 responses and vice versa from Th1 responses to Th0 or Th2 may be a desirable goal in future therapeutic strategies for allergic or DTH diseases, respectively. Immunization protocols that induce high levels of DTH are often associated with low levels of antibody production, while different protocols can produce the opposite effect (42). Recently, this concept has been applied to the control of experimental allergic encephalomyelitis (EAE), a classical, cell-mediated disease in rats and mice (12). The targeting of IgD-coupled myelin basic protein (MBP) on IgD-positive B cells, which make up a high proportion of rat B cells, prevented the induction of EAE. In this system, the MBP-targeted B cells, acting as APCs

for antigen-specific T cells, would favor antibody production and impede the cell-mediated response to MBP.

In conclusion, in the near future, our knowledge of the mechanisms of antigen recognition will allow us to take a rational approach to the manipulation of adverse immune responses.

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