Antigen Presentation to Lymphocytes

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flammation. Activation of CD8 + T cells results in cell-mediated immunity which is associated with the activation of CTLs that kill pathogen-infected cells. CTLs also render host cells resistant to viral infection and/or replication by secretion of cytokines such as tumour necrosis factor α (TNFα) and IFNγ.

Presentation of antigen by class I and class II MHC

CD8 + CTLs recognize peptide fragments bound to class I MHC molecules, whereas CD4 + helper T cells recognize them in association with class II MHC molecules (**Figure 1a,b**). Activation of cytotoxic and helper T cells, therefore, depends upon whether antigenic peptides are presented by class I or class II MHC molecules. It has been generally accepted that antigens derived from pathogens that reside intracellularly (endogenously) are usually presented to CD8 + CTLs in the context of class I MHC molecules. Presentation of endogenous antigens allows to the detection and destruction of pathogen-infected cells at an early stage of pathogen invasion before substantial replication of microorganisms can take place inside the host cells. On the other hand, extracellular antigens are usually taken up by endocytolytic pathways of APCs and presented to CD4 + helper T cells by class II MHC molecules.

The molecular mechanisms of antigen presentation by class I and class II MHC molecules are quite different. Presentation of endogenous cytosolic proteins by class I MHC molecules is mediated by a multicatalytic protease known as the proteasome. The translocation and binding of antigenic peptides to class I MHC molecules requires the transporter associated with antigen processing (TAP) (Koopmann *et al*., 1997). In contrast, class II MHC molecules present antigenic peptides derived from antigens internalized through the endocytic pathway. The assembly and the translocation of class II MHC molecules, and the binding of antigen to class II MHC depend on the function of the invariant chains (Pieters, 1997).

Presentation of exogenous antigens by class I MHC

Although in general, pathogen-encoded proteins produced inside an infected cell are presented in association with class I MHC molecules, exogenous antigens can also be presented by class I MHC molecules, especially when pathogen-encoded antigens are only expressed in non-haematopoietic cells (Sigal *et al*., 1999). These nonhaematopoietic cells, due to their low level of class I MHC expression and/or lack of costimulatory molecules, are unable to prime the antigen-specific CTLs. In this case, it appears that bone marrow-derived APCs acquire antigens exogenously and present the antigenic peptides to prime CTLs. Once the CTLs are activated, they can kill the viral-infected nonhaematopoietic cells. A potential source of the viral antigen may be virus-infected dead cells. Bone marrow-derived APCs may acquire viral antigens by phagocytosis of such dead cells and import them into the exogenous MHC class I pathway (Sigal *et al*., 1999).

Antigen presentation by CD1 molecules

In addition to MHC class I and II molecules, a novel lineage of antigen-presenting molecules, CD1, has recently been identified. CD1 molecules present lipid and glycolipid antigens to certain T-cell subpopulations including natural killer (NK) T cells and γδ T cells (**Figure 1c**). Although structurally more closely related to MHC class I molecules, CD1 molecules functionally resemble MHC class II in that they present lipid antigens derived by endocytic pathways (Sugita *et al*., 1998). Presentation of lipid antigens by CD1 complements the presentation of antigenic peptides by MHC molecules and allows the immune system to detect more diverse antigens of pathogen origin for host defence.

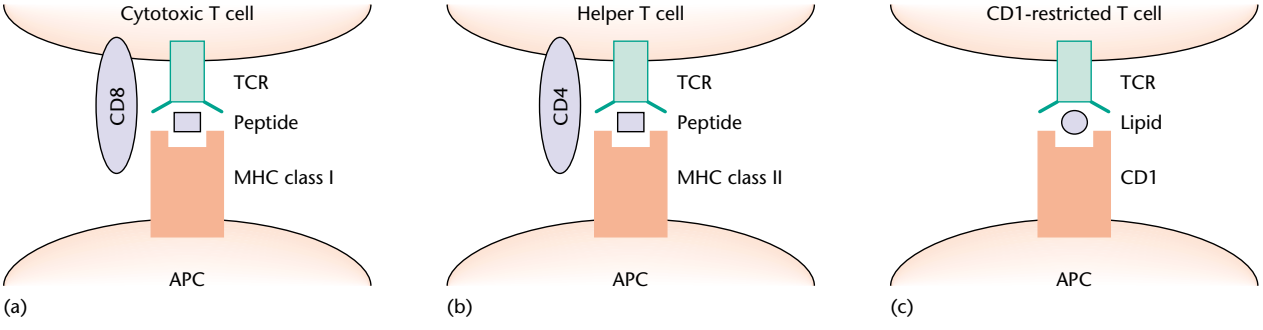

Figure 1 Antigen presentation to T lymphocytes. (a) CD8 + cytotoxic T cells recognize antigenic peptides presented by class I major histocompatibility complex (MHC) molecules. (b) CD4 + helper T cells recognize antigenic peptides presented by class II MHC molecules. (c) Certain T-cell populations, including natural killer (NK) T cells and γδ T cells, recognize lipid and glycolipid antigens presented by MHC-related molecules, CD1.

Presentation to B Cells

In general, B cells can directly recognize native antigens either in solution or on cell surfaces and therefore need no specific antigen-presenting cells to be activated. Antigen presentation to B cells by FDCs and macrophages, however, augments the immune response and is critical in the selection of high-affinity antigen-specific B cells (Kosco, 1991; Liu *et al*., 1997). In contrast to T cells, which recognize antigen-derived peptides bound to MHC molecules, B-cell recognition of native antigen or antigen epitopes is MHC-unrestricted.

Antigen presentation in germinal centres

Antigen presentation by FDCs localized in the B-cell compartment of primary follicles of lymphoid tissues plays an essential role in the activation, differentiation and apoptosis of B lymphocytes (**Figure 2**). Upon encounter with foreign antigens, germinal centres (GCs) develop where B cells undergo rapid proliferation and differentiation through interaction with cognate helper T cells. An important feature of GC B cells is that they undergo a process called somatic hypermutation by which their immunoglobulin gene variable regions are actively mutated in order to generate high-affinity antigen-reactive B cells. This process inevitably also generates numerous B cells that no longer recognize the foreign antigen or that recognize self antigens. Antigen presentation to B cells by FDCs plays a crucial role in the positive selection of high-affinity B cells and in the elimination of nonspecific, potentially self-reactive, B cells (Liu *et al*., 1997). FDCs in the B-cell compartment of GC trap and present antigens as immune complexes to GC B cells. GC B cells which bind antigens presented by FDCs through their B-cell antigen receptors (BCRs) receive a survival signal, in part, by upregulating the expression of the apoptosis-suppressing Bcl-XL gene product. Antigen-reactive GC B cells also ingest the antigen through their BCRs, process it and present it to helper T cells which then secrete cytokines to induce the proliferation and differentiation of B cells. By contrast, GC B cells unable to bind antigens die by Fas-dependent apoptosis. Antigen presentation to GC B cells by FDCs thus determines the fate of B cells and provides a mechanism to allow antigen-specific B cells to survive and differentiate while eliminating nonspecific B cells.

MHC class II negative marginal zone macrophages may present antigens to B cells and are involved in the induction of T-independent antibody responses. Interestingly, peritoneal macrophages are shown to present processed, but not native, antigens to B cells (Rizvi *et al*., 1989). In this case, both MHC class II antigen Ia + and Ia − macro-

thymic T cells. Developing thymic T cells that recognize self antigen–MHC complexes with moderate affinity are allowed to mature (a process called positive selection) while those recognizing self antigen–MHC complexes with high affinity are deleted to prevent the maturation of self-reactive T cells (a process called negative selection). It is unlikely, though, that thymic APCs can present all the self antigens to developing T cells for positive and negative selection. Those escaping negative selection are likely to be anergized in the periphery, in part through interaction with peripheral APCs that lack costimulatory molecules. Precise molecular mechanisms of positive and negative selection in thymus are described separately.

Other APCs

B lymphocytes found in spleen and lymph nodes are efficient APCs, especially when they recognize antigens. In this case, B cells can capture even minute quantities of antigens compared to other APCs (Townsend and Goodnow, 1998). Bone marrow-derived APCs appear to be required for the activation of cytotoxic T cells against viruses that infect nonhaematopoietic cells. Besides the APCs found in the lymphoid tissues, there are a large number of potential APCs in the body. These include Kupffer cells in the liver, microglias in brain, follicular cells in thyroid and fibroblasts in connective tissues and endothelial cells. Furthermore, other cell types may acquire the ability to present antigen if their MHC molecules are induced and expressed. Presentation of self antigens by such cells may be involved in the development of autoimmunity.

Activation versus Nonactivation

The consequence of antigen presentation to lymphocytes is influenced by several factors, including the site of presentation, the amount and avidity of antigens, and the presence or absence of costimulatory molecules expressed by APCs (Goodnow, 1996). Antigen presentation by APCs dictates the fate of developing T and B cells. T cells in the thymus recognizing self antigen–MHC complexes with high affinity are deleted. Likewise, immature B cells in the bone marrow that recognize self antigens with high affinity are eliminated. By contrast to thymus and bone marrow, in the periphery, T and B cells are activated if they recognize antigens with high affinity. The T or B cells recognizing antigens with low affinity are either nonresponsive or anergized. While intraperitoneal immunization of antigens induces an immune response, oral administration of the same antigen may induce anergy or peripheral tolerance against the antigen. The exact molecular mechanism for such differential responses remains obscure.

The amount and the avidity of antigens presented to lymphocytes also influence immune responses. Antigens presented in too small amounts or with too low avidity fail to induce negative selection of T cells in thymus and B cells in bone marrow, and may induce tolerance rather than an immune response in the periphery.

Costimulatory molecules on APCs

Expression of costimulatory molecules such as CD40 by APCs is essential in the activation of lymphocytes (Van Kooten and Banchereau, 1997). Antigen presentation by APCs stimulates T cells to express CD40 ligand, which then binds to CD40 expressed by APCs. CD40 ligation on APCs induces the expression of costimulatory molecules such as CD80 (B7-1) and CD86 (B7-2), which then further stimulate T-cell activation through interaction with CD28 on T cells. In the absence of CD40 or other accessory molecules, APCs have been shown to anergize T cells. Blockage of CD40–CD40 ligand interaction *in vivo*, as shown in either CD40- or CD40 ligand-deficient mice, abrogates humoral immune responses, demonstrating the significance of CD40 in initiating T-cell activation.

B cells as APCs

Although in general, antigen presentation by B cells is not as efficient as that by professional APCs, such as activated dendritic cells, B cells become efficient APCs when antigens can be recognized by the BCR. Resting B cells have been shown to induce partial activation or anergy of T cells under *in vitro* culture condition, while stimulation of B cells by CD40 ligand, BCR crosslinking or cytokines, greatly enhances the antigen presentation. Compared with other APCs, antigen-specific B cells can efficiently capture even small amounts of antigens through their BCR. In fact, it has been shown *in vitro* that activated, antigen-specific B cells present antigen to T cells and trigger proliferation and cytokine secretion. However, in marked contrast with *in vitro* studies, results from a number of *in vivo* studies have shown that B-cell presentation of antigen to cognate T cells induces tolerance or anergy rather than activation of T cells. Direct presentation of antigen by B cells or by transfer of antigen from antigen-specific B cells to endogenous antigen-presenting cells induces abortive proliferation of T cells. It appears that antigen presentation by B cells *in vivo* leads to the initial proliferation of T cells, which is followed by rapid disappearance of the T cells (Townsend and Goodnow, 1998).

In conclusion, APCs not only provide antigenic peptides in association with MHC molecules for T-cell recognition, but also regulate T-cell activation by supplying costimulatory signals. Antigen presentation thus constitutes a fundamental step in the initiation of an immune response. Further studies on the mechanisms of differential immune

responses triggered by different modes of antigen presentation should provide important clues in understanding and treating immunological disorders associated with dysregulated immune responses such as allergy and autoimmunity, as well as developing effective vaccines against various pathogens.

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