

Antigen-presenting Cells

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Antigen-presenting cells (APC) are able to acquire microbial and other antigens and display these antigens on their surface in a way that leads to activation of T and B lymphocytes, the major effector cells of the immune system. Different types of APC interact with different lymphocyte populations and stimulate distinct types of immune responses.

Introduction

Major 'effector cells' of the immune system, the T and B lymphocytes, cause the elimination of infected cells and the neutralization and removal of toxic materials. However, antigens such as viruses and bacteria do not stimulate specific effector lymphocytes directly. Instead, lymphocyte stimulation is achieved via antigens displayed on the surface of specialized cells that are called antigen-presenting cells (APC). Once 'memory' or 'effector' lymphocytes have been generated, following the initial processes of antigen presentation, a wide spectrum of cell types will present antigen to the activated cells. An expansion of the specifically responding lymphocyte populations may result as well as feedback on the cells presenting antigen, which may be further activated and/or killed.

Professional Versus Nonprofessional Cells

Cells that are specialized to initiate or promote the development of lymphocyte activation are often termed 'professional antigen-presenting cells'. The wider spectrum of tissue cells that can be stimulated to have antigen-presenting properties active in the development of secondary or effector functions have been termed nonprofessional antigen-presenting cells. Professional APC must possess the ability to acquire complex antigens from their environment, to process these into small components (usually peptides) suitable for presentation, and to express these components on the cell surface in a form that can be recognized by lymphocytes. In addition, they must be capable of delivering to the lymphocytes a range of additional signals that are able to enhance and modulate the activation of the responding cell. The interactions between multiple molecules on the surface of the APC and the lymphocyte occur in close proximity in regions of intimate contact between the two types of cells. Such regions have been termed 'immunological synapses'.

The term 'professional antigen-presenting cells' is usually used to describe dendritic cells, macrophages and

B lymphocytes; these cells are bone marrow-derived cells involved within the lymphoid tissues in stimulation of the effector lymphocytes of the immune response (**Figure 1**). They express MHC (major histocompatibility complex) molecules and have various other specialized characteristics, such as mechanisms for effective antigen uptake and expression of 'costimulatory' molecules that promote cellular interaction. However, the grouping together of these cells is artificial, since they serve different functions. Dendritic cells and their subsets are the only cells known to be potent in initiating primary immune responses. They can acquire and process a spectrum of antigens at the site of exposure in the peripheral tissues. Following this acquisition of antigen, they mature and migrate, carrying the antigens into the lymphoid tissues. Here subsets of dendritic cells may differentially cluster and activate different populations of antigenically naive lymphocytes that are located at that site, so shaping the type of immune response produced. The swollen lymph glands, a characteristic response to infection, bear witness to the way that this mechanism focuses the production of a variety of effector lymphocytes within specialized lymphoid tissues draining the site of infection. Macrophages and B cells participate as APC in the expansion of immune responses through their interactions with lymphocytes already responding to antigenic stimulation. They may not only deliver further stimulatory signals for the lymphocytes but also receive soluble mediators such as cytokines and chemokines from the stimulated cells that help promote their own development and function. Follicular dendritic cells can also be regarded as a type of professional APC. They are probably derived not from bone marrow but from fibroblastic reticulum cells in B cell areas of lymphoid tissues and are specialized APC for stimulating memory B cells. Once a response is established, B cells produce specific antibodies, and effector lymphocytes including cytotoxic T cells may be released and return to the sites of infection. Here, antigens such as viral antigens expressed on different tissues (**Figure 1**) in the context of MHC class I molecules, or on local class II molecules induced during inflammation, may now be presented to the effector lymphocytes, causing these presenting cells to act as targets for lysis or the action of locally produced cytokines

Introductory article

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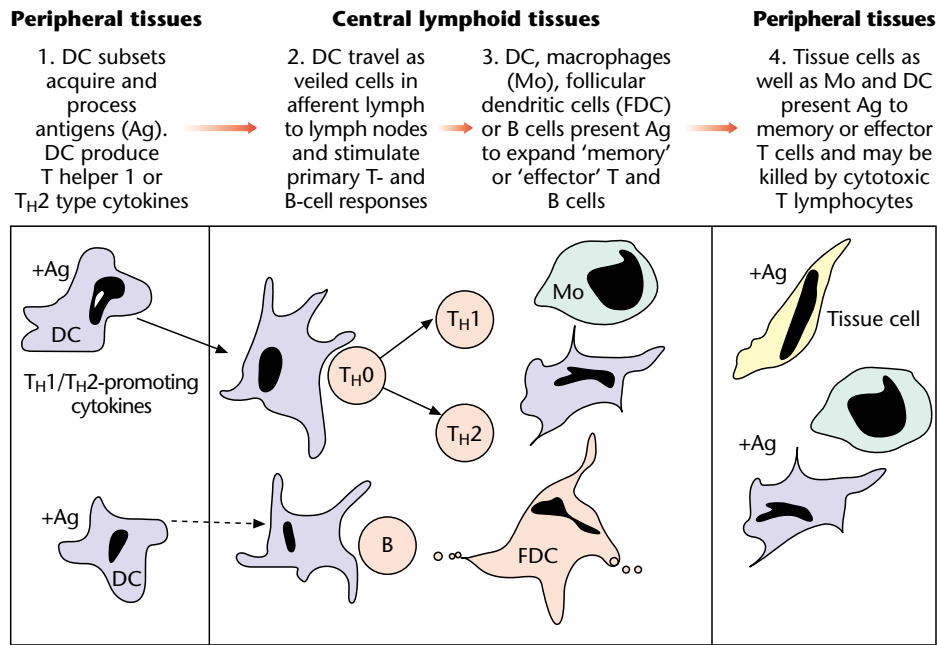


Figure 1 Antigen presentation in immune responses.

In conclusion, specialized antigen-presenting cells initiate primary responses in lymphocytes and receive signals from lymphocyte activation products. These interactions lead to expansion of both memory and effector T and B cells. In addition to antigen presentation by specialized cells, most tissues can develop recognition elements to focus activated lymphocytes, which can result in the removal of antigen-bearing cells.

Mechanisms of Presentation

The antigens presented on the surface of APC are often in the form of peptides derived from degraded protein antigens and associated with molecules of the major histocompatibility complex; this peptide–MHC complex engages receptors on T cells. If, as a result of viral infection for instance, antigens arise from within the cells (endogenous antigens), they tend to be presented in the context of MHC class I molecules that are expressed on the surface of most nucleated cells. Antigens expressed in this form stimulate a subpopulation of T cells (CD8 + cells) that can become killer or cytotoxic T lymphocytes. Exogenous antigens that are acquired by the cells from the extracellular environment can be presented in the context of MHC class II antigens, which have a more restricted distribution. These antigens stimulate T-helper cells (CD4 + cells), which can collaborate with B lymphocytes in stimulating antibody production, activate macrophages, or assist in the development of CD8 + T cells. There are some reports that dendritic cells (DC) can activate CD8 +

cytotoxic T lymphocytes (CTL) directly in the absence of 'help' provided by CD4 + cells, but in most situations dendritic cells probably interact with both CD4 + and CD8 + T cells (which probably occur together) within cell clusters. One feature that has traditionally distinguished dendritic cells from other APC *in vitro* is the ability to form clusters with antigenically naive T cells. Mature dendritic cells produce the chemokine DC-CK1, and possibly other similar mediators, which selectively attract naive T cells. *In vivo*, naive T cells entering the cortex of lymph nodes via high endothelial venules (HEV) interact transiently with a succession of DC which, in this locality, are often called interdigitating cells. Interactions between adhesion molecules such as DC-SIGN, ICAM-1, ICAM-2, LFA-1 and LFA-3 on the DC and ICAM-3, LFA-1 and CD2 on the T cell are involved in these interactions. In this way, naive T cells can scan many APC for antigen and dendritic cells select a specific T cell even when it is present at low frequency. In the presence of antigen, activation of T cells occurs, adhesion molecules are activated and the interactions are stabilized.

Signalling in the APC–lymphocyte clusters is not unidirectional; dendritic cells also receive signals from the T cells. CD40 ligand, induced on activated T cells, engages CD40 on DC and stimulates further maturation and production of cytokines, particularly IL-12. Soluble factors, such as 'TNF-related activation-induced cytokine' (TRANCE), produced by the T cells promote survival of the dendritic cells. In these cases, interactions between the ligand for CD40 on an activated CD4 + T cell and CD40 on the dendritic cells may be required before the dendritic cells can activate CD8 + cells.

Until recently it had been assumed that dendritic cells were only able to influence B-cell responses indirectly by stimulating 'helper' T cells. Dendritic cells form clusters with naive B cells and several recent studies have demonstrated that signals from dendritic cells can stimulate B-cell proliferation. Dendritic cells can cause the switch in the isotype of the antibody produced that occurs on B-cell maturation and influence the subclass of IgG antibody that these cells secrete. Interestingly, DC may also retain native antigen for prolonged periods of time making it available for recognition by B cells. Since initial activation of both naive T and B cells occurs in the 'T cell areas' of secondary lymphoid tissue, dendritic cells could select antigen-specific B cells from the recirculating pool in a way that is analogous to the selection of naive T cells discussed above. By doing so they would bring together two infrequent antigen-specific lymphocyte populations in a three-way T–B–DC interaction influencing the developing B-cell response both directly and indirectly. In addition to presenting antigens via classical MHC molecules, some antigen-presenting cells also express molecules related to the MHC molecules and referred to as 'nonclassical' MHC molecules such as CD1. These molecules may be important in presenting bacterially derived nonpeptide antigens such as lipids.

According to the two-signal model of T-cell activation, engagement of the T-cell receptor by the peptide–MHC complex ('signal 1') is not sufficient to activate the T cell; indeed, it may induce a state of anergy (in which T cells are refractive to subsequent stimulation). Additional signals ('signal 2') provided by costimulatory molecules on the surface of the APC are also required. The best-characterized of these are CD80 (B7-1) and CD86 (B7-2). The major ligand for these molecules on naive T cells is CD28. Engagement of CD28 upregulates the transcription of the gene for IL-2, a T cell growth factor, and stabilizes mRNA for IL-2. Once a T cell is activated, a second receptor with markedly higher affinity for CD80 and CD86 is induced. This is called CTLA-4 and delivers an inhibitory signal to the activated T cell and thus limits the proliferative response. Not all costimulatory activity can be accounted for by interaction with CD80 and CD86. Other APC molecules, including OX40L and CD40 which interact with OX40 and CD154 (CD40L) respectively, on the surface of the T cell can also deliver costimulatory signals.

Role in Immune Response

The role of specialist cells involved in the development of effector lymphocytes – dendritic cells, macrophages, B cells and follicular dendritic cells – will be described here. Since dendritic cells are the cells initiating the cascade of events that result in the development of immunity, this article will then focus particularly on ways in which variations in

subsets of dendritic cells, their maturation, migration and functional properties may determine the type of immune activity induced.

Brief description of specialized antigen-presenting cells

Dendritic cells (DC)

The extent and functional significance of lymphocyte heterogeneity has been delineated over several decades. In the same way, subpopulations of DC probably interact with different lymphocyte populations and play distinct roles in initiating responses in different lymphocyte subsets (Figure 2). Dendritic cells are the only cells unequivocally demonstrated to cause the aggregation and subsequent activation of T cells on their first exposure to an antigen. In addition, they are also potent APC for stimulating 'memory T cells' on re-exposure to the antigen. They are not homogeneous but are comprised of distinct subpopulations (Figure 2). Some DC can interact directly with B cells and may be involved in direct stimulation of primary B cell responses. Ultimately, all DC are derived from haematopoietic progenitors but they arise via multiple pathways of differentiation. A major distinction has been drawn between 'myeloid' and 'lymphoid' DC. Myeloid DC, identified as CD11c+ or CD8 α – subpopulations in humans and mice respectively, are closely related to monocytes/macrophages and require the growth factor granulocyte–macrophage colony-stimulating factor (GM-CSF) for their survival and differentiation. Some myeloid DC can develop from monocytes, whereas others derive from an earlier progenitor. In contrast, lymphoid DC (CD11c– or CD8 α +) may share progenitors with lymphocytes and natural killer (NK) cells; they are GM-CSF independent. The CD11c– DC population found in human peripheral blood expresses high levels of the lectin CD62L and have the potential to migrate directly to lymphoid tissue, where they are identified as 'plasmacytoid cells'. Langerhans' cells, the DC population in the epidermis, may represent a DC lineage that is dependent upon the cytokine TGF β for development *in vivo*. In addition, there are also reports that pre-B cells and precursors of neutrophils can differentiate into cells with the properties of DC when cultured in appropriate cytokine conditions. The functional differences between the DC subsets that are currently recognized are discussed in more detail later.

The molecular basis of dendritic cells' remarkable potency and their ability to activate naive T cells is not fully understood. Most of the molecules on DC that are involved in antigen presentation are not unique to this type of APC, although they are often expressed at particularly high levels on DC. However, a DC-specific lectin, termed DC sign, with high affinity for ICAM-3 on the surface of naive T cells has recently been described and this may play

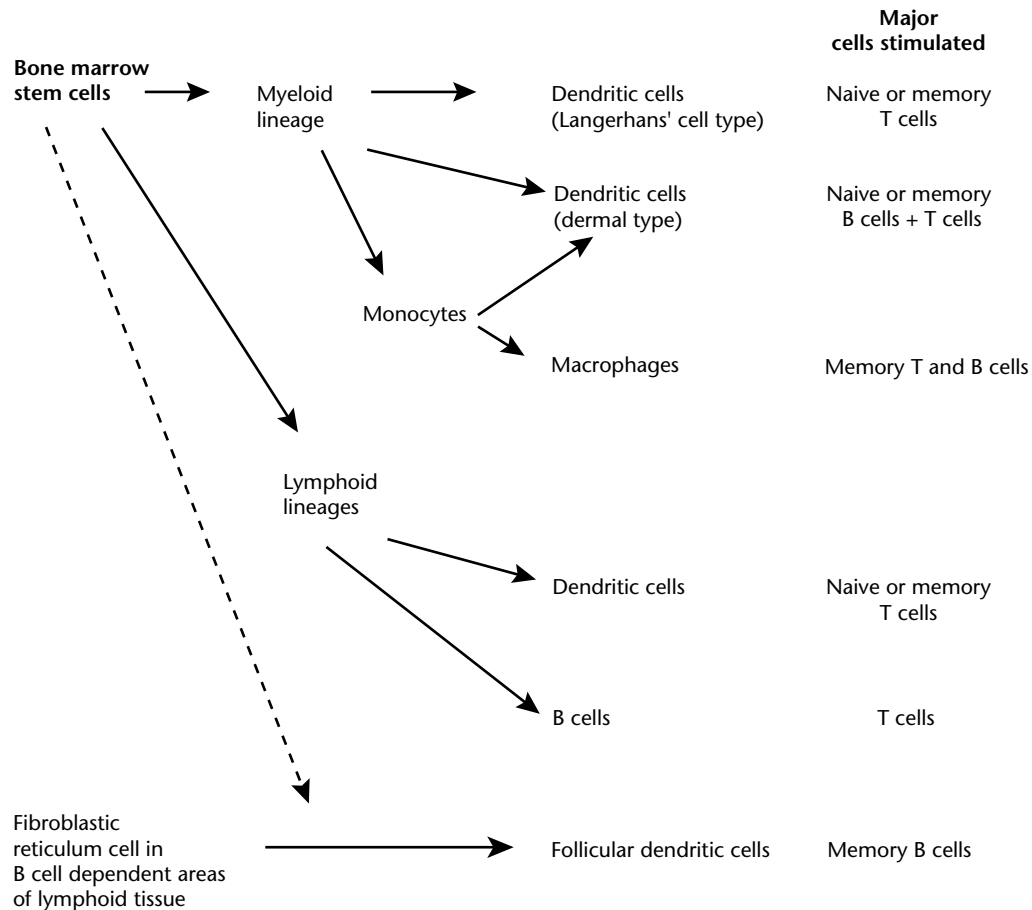


Figure 2 Comparison of different specialist antigen-presenting cells and the cells with which they interact.

a crucial role in stabilizing the initial interaction between DC and resting T cells.

B cells

Resting B cells constitutively express high levels of cell surface MHC class II but do not appear capable of stimulating primary T-cell responses. Resting B cells do not express costimulatory molecules necessary for efficient antigen presentation, but these molecules are induced upon activation; these activated B cells are more potent APC. Antibodies on B cells in the form of cell surface immunoglobulins function as specific antigen receptors. The capture and presentation of soluble protein antigens by this route is highly efficient, but the presentation of antigens captured nonspecifically is not. B cells expressing a particular receptor are estimated to have a frequency of between 1 in 10⁴ and 1 in 10⁶ in a naive individual and this low frequency may limit severely the ability of B cells to function as APC in the earliest stages of an immune response. Instead, the role of antigen presentation by B cells is probably to capture antigen via surface immunoglobulin and present linked T-cell epitopes to preactivated T cells during an ongoing response. This is termed linked

recognition and it also enables the B cell to elicit the growth and differentiation signals known as ‘help’ from the T cell. Initially this interaction occurs in primary foci of B-cell proliferation in predominantly T cell areas of lymph nodes. It involves the induction of the ligand for the molecule CD40 and this molecule can engage CD40 expressed on the resting B cell. Adhesion molecules (LFA-1 on the T cell and ICAM-1 on the B cell) stabilize a tight interaction between the lymphocytes, which is followed by cytoskeletal reorganization and the polarized release of the cytokine interleukin (IL)-4. Thus, soluble signals from the T cell are targeted to the specific B cell. The combination of signalling through CD40 and IL-4 drives clonal expansion of the B cells. The potential role of other APC populations in facilitating these interactions is discussed below. Subsequent interactions between B and T cells in the germinal centre are also involved in the generation of B-cell memory.

Macrophages

Macrophages take up a variety of antigens and intracellular degradation of these is a pathway of removal in the absence of an adaptive immune response. They express a

number of receptors including the macrophage mannose receptor and the scavenger receptor that recognize components of microbes. Once bound, these organisms are engulfed in a process termed phagocytosis and degraded. Such mechanisms are particularly important for the removal of bacteria. Macrophages normally express low levels of MHC class II molecules and costimulatory molecules, but these are upregulated by a number of microbial products. Many of the macrophage molecules are yet to be characterized, but in the case of bacterial endotoxin (lipopolysaccharide, LPS) the molecule CD14 may bind complexes of LPS and LPS-binding protein. A molecule called Toll-like receptor 4 (TLR4), so-called because of its homology to the Toll protein of the *Drosophila* fruitfly, appears to be involved in transmitting this signal into the cell. The end result is that antigens generated from the degraded microbes can be presented to specific T cells. This presentation drives local expansion of T cells but, most importantly, elicits from the T-cell signals that cause activation of the macrophage and dramatically upregulate its microbicidal activity.

A number of pathogenic bacteria and parasites have evolved mechanisms to enable them to survive within the hostile environment of the macrophage. Indeed, for some, the macrophage is the main host cell that they infect. Only a macrophage that is activated to a microbicidal state can eliminate such pathogens, and the feedback from T cells following antigen presentation by the macrophages is essential. The most important mechanism is the generation of products that are directly toxic to the microbe. These include nitric oxide (NO), produced by the enzyme inducible NO synthase (iNOS), and toxic oxygen metabolites including superoxide and hydrogen peroxide. Other mechanisms include enzymes such as lysozyme that can degrade the cell walls of Gram-positive bacteria, the production of antimicrobial peptides (e.g. defensins) and metabolic competitors like lactoferrin, which binds iron. Macrophages are activated primarily by interferon γ (IFN γ) produced when a specific CD4⁺ T helper (T_H1) cell recognizes antigen on the surface of an infected macrophage. Activation also upregulates receptors for TNF α , and the autocrine production of TNF following stimulation by microbial products combines with interactions between CD40 on the macrophage and CD40 ligand on the activated T cell to maximize activation. Although they are toxic to bacteria, prolonged or uncontrolled production of many of these agents would also be damaging the host. The need to elicit activating factors by presenting antigen to specific T cells means that cytokine production is restricted to the local environment and activation is targeted only to infected cells.

Follicular dendritic cells (FDC)

Follicular dendritic cells form a specialized and unusual APC population. They do not synthesize MHC class II

antigens but may passively acquire them. Their origin has been controversial, but they appear not to be bone marrow-derived but to develop locally from fibroblastic reticular cells in the B cell areas of lymphoid tissue. There may be a requirement for signals provided by bone marrow-derived cell populations for their development (**Figure 2**). They are localized primarily in the light zone of germinal centres and have the ability to hold intact antigens on their surface for long periods ranging from months even to years. They express Fc and complement receptors and some antigenic material is in the form of antigen–antibody complexes. FDC are involved in the presentation of antigen to B cells and the maturation of the antibodies of the humoral immune response, but their properties are poorly understood. In the process known as affinity maturation, they may select and promote the survival of B cells with receptors of high affinity for the antigen on the FDC surface. B cells with these receptors, which are generated by somatic hypermutation, survive and go on to produce antibody or become memory cells. Those with low-affinity receptors die.

Further properties of specialized antigen-presenting cells

Tissue surveillance

The majority of pathogens invade the host via a mucosal surface or the skin, whereas activation of antigenically naive T cells occurs in secondary lymphoid tissue. Therefore a mechanism is required whereby antigen, APC and T cells are brought together in such tissue (**Figure 1**). Dendritic cells provide this mechanism. They are present in most tissues of the body, where they acquire antigen and transport it to the draining lymph nodes; here they are able to interact with cells from the recirculating pool of naive T cells. Because of this activity, DC are sometimes called the sentinels of the immune system. Under normal circumstances, DC are present in the tissues only in small numbers, but additional cells are recruited rapidly in response to inflammatory signals – particularly to chemokines such as IL-8, MIP-1 α , MCP-1 and RANTES. Dendritic cell progenitors in the blood are continually tethered to and rolling along vascular endothelia, poised to enter the tissues in response to such signals. These progenitors may include monocytes and undifferentiated precursors in addition to the circulating DC population that is identifiable in peripheral blood. The molecules involved in the interaction between DC and vascular endothelia are not well characterized but, in the skin, binding to endothelial P- and E-selectin by P-selectin glycoprotein ligand (PSGL)-1 has been implicated.

Antigen uptake and processing

Dendritic cells in the tissues are an immature population, highly adapted for another important requirement of

specialized APC, namely efficient uptake of antigen. Immature DC are phagocytically active and internalize fluid-phase antigens by macropinocytosis. Dendritic cells express receptors for the Fc portion of immunoglobulin molecules and for complement components and these facilitate the uptake of opsonized particles. They also express receptors that allow them to recognize types of molecules or 'patterns' characteristic of microbes. In this way they are able broadly to distinguish potentially dangerous nonself antigens. These receptors may include molecules that recognize mannose and other carbohydrates or the unmethylated CpG motifs that are characteristic of prokaryotic DNA. The molecule DEC205, recognized by the DC-reactive monoclonal antibody NLDC-145, is probably one such receptor. Dendritic cells are also efficient at taking up apoptotic cells and acquiring antigens they bear. This allows DC to mediate the phenomenon called cross-stimulation or cross-priming.

Much has been learnt about the cell biology of antigen processing and this is discussed in detail elsewhere.

Transport to lymphoid tissue

Following exposure to antigen, DC migrate to the draining lymph node. During this process they undergo maturation; they downregulate the machinery required for antigen uptake and acquire their characteristic ability to cluster and stimulate T cells. This process involves upregulation of MHC class II expression and redistribution of MHC–antigen complexes to the cell surface as well as upregulation of the expression of molecules such as CD80, CD86 and CD40. This requirement for maturation and migration from peripheral tissues to the lymph nodes before stimulatory activity is acquired probably helps provide protection against excessive inflammation or autoimmunity induced in tissues by stimulation of memory T cells by cross-reactive self-antigens on DC.

The signals that trigger DC maturation or migration are not fully understood but include cytokines, such as tumour necrosis factor α (TNF α), which signal the presence of danger and the direct action of microbial products such as lipopolysaccharide or dsRNA. In response to maturational stimuli, DC change their cell surface expression of chemokine receptors from those that bind inflammatory chemokines to those that bind constitutively produced chemokines. Thus, production of secondary lymphoid chemokine (SLC) by the endothelial cells of lymphatic vessels and of Epstein–Barr virus-induced molecule 1 ligand (ELC) by mature DC that have previously migrated to the lymph node helps direct maturing DC into the T cell areas of the lymph node.

Shaping of the immune response by cytokines of APC

APC, and in particular DC, occupy a pivotal position at the intersection of innate and acquired immunity and as such are ideally placed to shape the developing response.

The cytokines produced by these APC determine what type of immune response is produced (**Figure 1**). However, the 'default' pattern of DC cytokine production varies between cells of different lineages and between cells isolated from different tissues. In addition this 'default' pattern is not fixed but can be modified in response to cytokines or microbial stimulation. T helper cells of type 1 (T_H1) mediate preferentially cell-mediated immune responses that include the development of macrophage activation and cytotoxic T lymphocytes, whereas T_H2 cells favour immune responses functioning predominantly via antibody-mediated mechanisms. The production of cytokines such as IL-12 and IL-10 by DC may promote the development of T_H1 and T_H2 responses, respectively. Although IL-12 was classically regarded as a macrophage-derived cytokine, recent experiments show that DC may be the major source of IL-12 in the early stages of an immune response.

Some workers have termed DC that drive T_H1 responses as DC1 and those that drive T_H2 responses as DC2. It is not yet clear whether these two populations correspond directly to lymphoid and myeloid DC populations. On the one hand, several studies have shown that lymphoid DC predominantly produce IL-12 and preferentially stimulate T_H1 responses, whereas myeloid DC produce less IL-12 and more IL-10 and stimulate T_H2 responses. On the other hand, another study with human cells has described the reverse, with myeloid DC being the major stimulators of T_H1 responses. DC and their stem cell precursors also express receptors for many cytokines. Thus, IL-12 can activate DC through IL-12 receptors. Once produced by DC, IL-12 may thus have an 'autocrine' effect by feeding back onto the DC to enhance further IL-12 production. Other autocrine pathways (e.g. with IL-4) may help to consolidate particular cytokine profiles within DC although such pathways have not yet been formally identified. Potential negative feedback mechanisms may also exist. For example, excessive doses of the T_H2-promoting cytokine IL-4 inhibit the survival of a T_H2-promoting DC population.

Dendritic cell populations isolated from Peyer's patches in the gut (which contain both lymphoid and myeloid populations) or from the airway epithelium, when compared with DC from spleens, produce more IL-10 and have a greater tendency to stimulate T_H2 responses. The tendency of nonreplicating antigens to stimulate T_H2 responses when administered to mucosal surfaces probably reflects this 'default' pattern of cytokine production by DC at these surfaces. However, much of the variability of DC cytokine patterns may be explained by the way in which they are influenced by exposure to antigens. Thus, mucosal DC can be switched by inflammatory stimuli to the production of IL-12 and the stimulation of T_H1 responses. Presumably this switch underlies the ability of the host to mount T_H1 responses, such as IFN γ production, in response to challenge by mucosal pathogens.

Recently, infection of DC with an immunosuppressive retrovirus was shown to induce a switch from the production of IL-12 to the production of IL-4 by the DC. In addition, a series of new experiments have indicated that the DC that acquires an antigen and the DC that presents it to T cells need not be the same cell; antigen can be transferred between dendritic cells. The signals provided during the interaction between DC and those provided by the second DC could both be important in influencing the developing T-cell response.

APC and nonresponsiveness

Specialized APC may be involved in both 'central' and 'peripheral' tolerance by delivering signals that induce nonresponsiveness, particularly to self-antigens, established both during T-cell generation in the thymus and later outside the thymus. In the thymus, epithelial cells, and possibly DC under some circumstances, cause the positive selection of T-cell populations for export to the circulation to form the peripheral pool of T cells. In addition, T cells specific for ubiquitous self-antigens are deleted in a process known as negative selection. This stage of negative selection of the T-cell repertoire is usually mediated by DC. The positive or negative effects of interaction of APC with thymocytes or mature T cells may reflect differences in the dose and distribution of antigens present in maturation states of the responding T-cell populations or in features of the microenvironment. However, thymic DC may have inherent tolerogenic activity. CD8⁺ lymphoid DC predominate in the mouse thymus and this population (but not CD8⁻ DC) has been shown to induce both Fas-mediated apoptosis and activation in CD4⁺ T cells. This has led some to suggest that, in general, lymphoid DC represent a regulatory or tolerogenic population.

Although the majority of potentially self-reactive T cells are eliminated in the thymus, those with receptors that recognize self determinants that are not expressed in the thymus escape this process and migrate into the periphery. Additional mechanisms are required to prevent the development of autoimmunity. In some cases the self antigen seems to be ignored by the immune system, but in others an active process in which autoreactive T cells are removed or rendered anergic is involved. A phenomenon has been recently described in which APC acquire antigens expressed in nonlymphoid tissues and then induce antigen-specific anergy or deletion in the draining lymph nodes. Responses of both CD4⁺ and CD8⁺ T cells can be affected. This process has been termed 'cross-tolerance' by analogy to the process of 'cross-priming' described earlier. The nature of the APC has not been determined, but the cell is bone marrow-derived. Interestingly, T-cell activation and proliferation precede tolerance in these models, suggesting that the APC is likely also to possess the characteristics of specialized stimulatory APC. Many

workers favour a role for a DC population, possibly of the lymphoid subset.

There is thus mounting evidence that DC, and possibly other specialized APC, can be either stimulatory or tolerogenic and that treatments that either remove subpopulations of DC or boost their numbers can regulate the balance between these outcomes. However, it is not yet clear whether stimulation and tolerance are mediated by different cell populations, by the same cell populations responding to different signals in their environment, or by a combination of both of these. One idea is that DC continually migrate with antigen into lymph nodes but that in the absence of inflammation and the consequential upregulation of costimulatory molecules they induce or maintain tolerance. However, this simple model is not consistent with the T-cell activation seen in the 'cross-tolerance' experiments. On the other hand, perhaps only lymphoid DC with inherent tolerogenic activity can gain access to T cell areas of lymphoid tissue under steady state conditions. Only under inflammatory conditions are stimulatory myeloid DC able to gain access to these areas. This view is supported by the observation that, prior to exposure to antigen, lymphoid DC are the predominant population in T cell areas. The distribution of antigens on different DC populations and interactions between DC themselves may also be central to the final outcome.

APC and survival of mature T cells

Several studies now suggest that, in addition to positive selection of thymocytes on epithelial cells bearing MHC class I and class II antigens, long-term survival of mature T cells requires engagement of MHC molecules in the periphery. Experiments with transgenic mice suggest that expression of MHC class II on DC is sufficient to allow this long-term survival of CD4⁺ T cells.

Elimination of antigen-bearing APC

Dendritic cells are not usually found in efferent lymphatics, which suggests that they are eliminated in the lymph nodes. They may undergo apoptosis or be eliminated in an interaction with NK cells or with antigen-specific cytotoxic T lymphocytes. Whatever the mechanism, elimination of antigen-bearing DC may be an important component of the natural downregulation and termination of the response.

Conclusions

Dendritic cells, B cells and macrophages have been termed 'professional antigen-presenting cells' and all three cell types can present antigens to restimulate memory or effector T lymphocytes. However, only dendritic cells are efficient at stimulating antigenically naive T and B cells to initiate a primary immune response. B cells present

antigens and elicit antigen-specific differentiation signals from T cells, which results in production of specific antibodies by the B cells. Macrophages can also present antigens to responding lymphocytes, which, in turn, deliver locally acting activation signals that aid their role in phagocytosing and destroying bacteria. Follicular dendritic cells are specialized to promote B cell memory responses. Finally, a wide spectrum of tissues can present antigens to activated T cells and this interaction may result in the cytotoxic killing of the antigen-presenting cell.

Now that it is established that dendritic cells are the initiators of immune responses, understanding of the influence of the dendritic cell in initiating these responses is still in its infancy. The 'decision' to make an immune response may be made when DC acquire antigen, mature and migrate into the draining lymph nodes. The dendritic cell subset and its properties, such as the cytokine profile, may determine not only whether there is an immune response but also what type of lymphocytes are stimulated and consequently the scope of the immune activity produced. Dendritic cells are, therefore, central to the production of protective immunity, and changes in the properties of dendritic cells are involved in the develop-

ment of immunologically based diseases. Therapies that act on dendritic cells are already being developed for diseases such as cancer and autoimmunity.

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