**Dendritic Cells and Antigen Processing**

In order to trigger adaptive immunity, a sample of foreign material must first be captured, processed, and presented in the correct fashion to cells that can recognize it. This is the responsibility of antigen-processing cells.

Processing involves breaking large protein molecules into small peptides within a cell. These peptides are then attached to specialized antigen-presenting receptors called major histocompatibility complex (MHC) molecules. The peptides bound to MHC molecules are then carried to the cell surface.

Adaptive immunity is triggered when these MHC-bound peptides are recognized by specific receptors on lymphocytes.

These lymphocytes (called T cells) bind and respond only to peptides that have been correctly processed and presented. This ensures that adaptive immune responses do not proceed indiscriminately.

The organisms that trigger adaptive immune responses are of two general types. One type is typified by the bacteria that invade the body from outside and then grow in the tissues and extracellular fluid. Their antigens are called exogenous antigens, and they are processed by specialized antigen-processing cells.

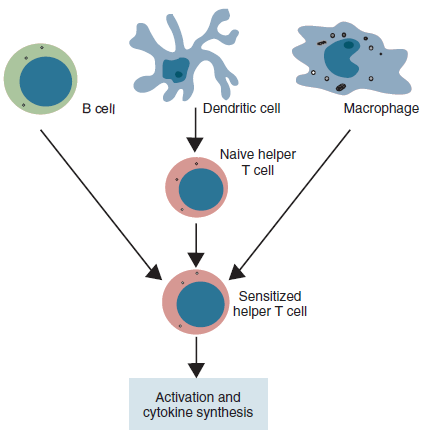
A second type of invading organism is typified by viruses that invade a cell and force it to make viral proteins. These new proteins are called endogenous antigens. Endogenous antigens are processed by the cells in which they are produced.

There are two classes of MHC molecules called MHC class I and MHC class II. MHC class I molecules are made by all nucleated cells and bind endogenous antigens. MHC class II molecules, in contrast, are restricted to specialized antigen-processing cells and bind exogenous antigens. The body mainly employs three cell types: dendritic cells, macrophages, and B cells to process exogenous antigens. The most important of these are dendritic cells (Figure 10-1).

**Dendritic cells**

It perform three major functions. First, they serve as sentinel cells and activate innate defenses when they first encounter invaders. Second, they process exogenous antigens and thus initiate adaptive immune responses. Third, they can regulate adaptive immunity by determining whether an antigen will trigger an antibody-mediated or a cell-mediated response.

Dendritic cells are at least 100 times more effective antigen presenting cells than macrophages or B cells. Dendritic cells can take up many different antigens, including dead microorganisms, soluble antigens in tissue fluids, and antigens released by dying cells, and present them to T cells. Dendritic cells are the only antigen-processing cells that can activate those T cells that have never previously encountered an antigen (naïve cells) and therefore are essential for initiating primary immune responses.



**Subpopulations**

Dendritic cells are a mixture of several different subpopulations. Thus they are divided into myeloid (M-DC) and plasmacytoid (P-DC) dendritic cells (Figure 10-3). These two subpopulations differ in morphology, in surface antigens, and in their functions, although they share adhesion molecules, co-stimulatory molecules, and activation markers. Other specialized

dendritic cell subpopulations are found in the skin (Langerhans cells) and in lymphoid organs (follicular dendritic cells).

As pointed out earlier, the adaptive immune system has two major branches: the antibody-mediated and cell-mediated immune responses. The type of immune response mounted by an animal is determined by the type of helper T (Th) cells triggered in response to an antigen. Thus there are several types of Th cells (see Figure 14-2). One major type, Th1 cells, stimulates cell-mediated immune responses designed to protect animals against intracellular organisms. The other major type, Th2 cells, stimulates antibody-mediated immune responses designed to protect animals against extracellular invaders.

Which Th cell type is activated depends on the use of different dendritic cell subpopulations.

**Myeloid Dendritic Cells**

Blood monocytes are the immediate precursors of both tissue macrophages and M-DCs. Which of these cell types is produced depends on the mixture of cytokines and cells encountered by the monocyte as it differentiates. Each cell type can convert to the other until late in the differentiation process. M-DCs can therefore be considered part of the mononuclear phagocytic system being derived from a common stem cell, respond to the same growth factors, express the same surface markers, and in effect are in no specific way uniquely different from other macrophages. Thus macrophages may consist of a spectrum of cell types ranging from highly effective antigen presenters (dendritic cells) at one extreme to suppressors of T cell activation (M2 cells) at the other. Monocytes exposed to certain T cell cytokines differentiate into M-DCs, and functionally different dendritic cells can be induced according to the local cytokine environment.

Bovine peripheral blood monocytes exposed to staphylococcal enterotoxin C1, a superantigen (Chapter 14), will convert to dendritic cells.

**Plasmacytoid Dendritic Cells**

P-DCs are long-lived cells found in blood, bone marrow, and lymphoid organs. They arespecialized to respond to viruses by producing massive amounts of the type I interferons (IFN-α and IFN-β). Their numbers increase during infection. It is possible that the P-DCs serve as an early warning system for viral infections since they are rapidly activated by viral nucleic acids. Plasmacytoid dendritic cells have a unique ability to link innate and adaptive immunity. After producing large amounts of type I interferon, they are still able to differentiate into mature DCs that can stimulate naïve T cells. Because P-DCs secrete large amounts of IFN-α, they also activate natural killer (NK) cells .

**Dendritic Cell Maturation**

Although many subpopulations of dendritic cells have been characterized, their most important division is based on their state of maturity (Figure 10-5). Thus immature dendritic cells are highly specialized and efficient antigen-trapping cells. As they mature, dendritic cells undergo cellular reorganization and become specialized and efficient antigen presenting cells.

**Immature Dendritic** **Cells**

Newly generated M-DCs migrate from the bone marrow through the blood to lymph nodes or tissues. Here they act as “sentinels” whose role is to capture invading microbes. With their short life span, they can be regarded as disposable antigen-trapping cells. If they do not encounter antigens, they die in a few days. If, however, they encounter antigens and are stimulated by tissue damage or inflammation, they become activated and mature rapidly.

Immature dendritic cells have receptors that help them carry out their functions. These include cytokine receptors such as interleukin-1 receptor (IL-1R) and tumor necrosis factor receptor (TNFR), chemokine receptors; C-type lectins, Fc receptors (FcγR and FcεR), mannose receptors (CD206), heat-shock protein receptors, and TLRs.

Although the most important functions of dendritic cells are to trap, process, and present antigen to the cells of the immune system, they must also be able to kill any pathogens they encounter. Thus dendritic cells produce NADPH oxidase (NOX) and can kill invaders by mounting a respiratory burst. Activation of TLRs by pathogen-associated molecular patterns (PAMPs) enhances their production of superoxide.

Dendritic cells mature in response to interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) as well as to PAMPs and damage-associated molecular patterns (DAMPs). Injured and inflamed tissues release large amounts of soluble heparin sulfate that binds to TLR4 and activates dendritic cells. Breakdown of nucleic acids generates uric acid, another potent dendritic cell activator. One of the most important activators of immature dendritic cells is high mobility group box protein-1 (HMGB1). Immature dendritic cells are attracted to areas of inflammation by chemokines, defensins, and HMGB1.

Immature dendritic cells specialize in capturing antigens and cell fragments by phagocytosis, by pinocytosis , and by interaction with various cell surface receptors. They also capture apoptotic cell bodies. If they ingest bacteria, they can usually kill them. They can distinguish between normal tissue debris and foreign organisms by selectively sampling their environment. This differentiation depends on the ability of the foreign material to bind to TLRs. Activation of TLRs by PAMPs ensures that ingested material is processed in such a way that it triggers adaptive immunity. Material that does not activate TLRs is not processed and will not trigger an adaptive response.

The phagosomal contents of conventional phagocytic cells such as neutrophils and macrophages are very acidic and hence optimized for proteolytic destruction of foreign material. The pH within dendritic cell and B cell phagosomes is in contrast relatively alkaline since these phagosomes do not fuse with lysosomes. Cysteine and aspartyl proteases are inhibited at these high pH levels, and as a result, antigen is not completely degraded but rather is preserved for presentation on MHC class I molecules.

**Mature Dendritic Cells**

After they have captured and processed antigens, immature dendritic cells carry these antigens to sites where they can be recognized by T cells. The activated DCs are attracted to lymphoid organs by the chemokine CCL20. Infection or tissue damage also promotes the migration of antigen-bearing dendritic cells to lymph nodes or the spleen. Once they enter a lymphoid organ, the cells mature rapidly.

Mature dendritic cells secrete the chemokine CCL22. This attracts T cells, which accumulate in clusters around the dendritic cell (Figure 10-6). The dendritic cells embrace the T cells in a net of dendrites as they interact. During this time, the T cells examine the mature dendritic cells for the presence of antigen fragments. If their antigen receptors can bind the presented fragments, the T cells will be triggered to respond.

As dendritic cells mature, their MHC molecules move from intracellular endosomes and lysosomes to the cell surface. Cell surface expression of their co-stimulatory molecules also increases. As a result, MHC molecules and MHC-peptide complexes are found at levels 100 times higher on mature dendritic cells than on other cell types such as B cells or macrophages. Their expression of co-stimulatory molecules such as CD86 (Chapter 14) may also rise 100-fold.

Mature dendritic cells are the only cells that can trigger a primary T cell response. One reason for this is that mature dendritic cells can assemble complete T cell activation complexes (antigen-loaded MHC plus co-stimulatory molecules) within the cell before they are carried to the cell surface. Mature dendritic cells also express DC-SIGN (CD209), a C-type lectin, that binds a ligand called intercellular adhesion molecule-3 (ICAM-3 or CD50) on naïve T cells. DC-SIGN thus permits transient binding between dendritic cells and T cells. It permits a single dendritic cell to rapidly screen thousands of T cells to find the few that are expressing a compatible antigen receptor. Because of their potency, only a few dendritic cells are needed to trigger a strong T cell response. Thus one dendritic cell may activate as many as 3000 T cells.