Cells of the Immune System

Introductory article

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A variety of cell types are important components of the immune system. They constitute some of the body's main defences against infection.

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Introduction

The main function of the immune system is to defend the body against a wide variety of pathogenic infectious agents with vastly differing natures, i.e. viruses, bacteria, fungi, protozoa and parasitic worms. The complexity of this task requires a sophisticated repertoire of mechanisms for the recognition of, and defence of the body against, these pathogens. This is achieved by an array of cells (and molecules which they secrete) which are dispersed throughout the body and collectively constitute the immune system.

Most of the major cell types of the immune system are derived from progenitors (stem cells) in the bone marrow. Many of the mature cells circulate in the bloodstream and are dispersed throughout tissues of the body, while some also congregate in specialized lymphoid tissues. Furthermore, in order to generate effective immunity, the various cell types cooperate with each other by means of direct interactions between cell surface molecules and via the molecules that they secrete.

As summarized in **Table 1**, a number of criteria can be used to distinguish between different cell types of the immune system: these include developmental relationships, phenotypic distinctions based on morphology or cell surface molecules (e.g. CD markers), and functional attributes.

Lymphocytes

The three major types of lymphocytes are called B cells, T cells and NK (natural killer) cells. They arise from lymphoid progenitors in the bone marrow: mammalian B cells fully develop here, whereas T cell precursors migrate to the thymus for selection and maturation. The bone marrow and thymus are thus known as primary lymphoid organs. Mature B and T cells circulate in the bloodstream and lymphatic system, spending some time in the secondary lymphoid tissues, i.e. the spleen, lymph nodes and mucosa-associated lymphoid tissues (MALT). Two morphological types of resting lymphocytes can be distinguished: B cells and the majority of T cells are small lymphocytes with a thin rim of cytoplasm surrounding the nucleus, whereas NK cells and some T cells are larger, have more cytoplasm and distinct cytoplasmic granules, and are known as large granular lymphocytes (LGLs).

B and T lymphocytes are entirely responsible for adaptive or acquired immunity, i.e. the ability to recognize each pathogen in a specific way and to mount a faster and bigger response on repeated exposure to a particular pathogen (immunological memory). This is because B and T cells express surface receptors which specifically bind to materials that are foreign to the body (known as antigens). The receptors of a single lymphocyte are identical to each other and recognize a single antigen. However, millions of different antigen receptors are collectively expressed by the whole population of lymphocytes in the human body, thus conferring the ability to recognize a great many foreign antigens. A lymphocyte can be activated when it binds an antigen for which its receptors are specific, causing it to become an enlarged, dividing lymphoblast. Some of the progeny differentiate into short-lived effectors of the immune response while others become long-lasting memory cells which will be reactivated if there is subsequent exposure to the same antigen.

B lymphocytes

The B cells constitute 5–15% of human blood lymphocytes. The main function of a B cell is to secrete soluble recognition molecules called antibodies which specifically bind to an antigen recognized by that B cell. These antibodies (also known as immunoglobulins) are, in fact, the secreted form of a B cell's surface antigen receptors and bind to exactly the same antigen (**Figure 1**). A B cell will only produce antibodies when it has been activated by binding antigen; this activation process also usually requires help from T cells. The activated B cell undergoes multiple divisions and some of the resulting cells differentiate into antibody-secreting cells. These are known as plasma cells, and they possess copious rough endoplasmic reticulum involved in antibody synthesis.

During activation, B cells can undergo two types of genetic changes that modify the nature of the antibodies

Table 1 Cells of the immune system and their relationships

Developmental origin	Morphology	Cell types	Main functions	
Lymphoid	Mononuclear	NK cells	Cytotoxicity	
		CD8+ T cells		
		CD4+ T cells	Regulation	
		γδ-T cells		
		B cells	Antibody production	Antigen presentation
		Dendritic cells		
		Monocytes/macrophages	Phagocytosis and killing	
Myeloid	PMN*/Granulocytes	Neutrophils		
		Eosinophils	Extracellular digestion	
		Basophils	Inflammation	
		Mast cells		

*PMN, polymorphonuclear leucocytes.

they produce. First, they can change their antigen-binding properties by a process called somatic mutation, so that some B cells (and their antibodies) bind more strongly to their specific antigen. Secondly, they can change their immunoglobulin class (which is initially IgM and IgD) to produce antibodies with different biological effector functions (IgG, IgA or IgE). The main structural difference between antibodies of different classes is in the nonantigen-binding portion of the molecules, called the Fc region, which is constant in structure between antibodies of the same class produced by different B cells. Various cell types of the immune system which do not themselves have antigen-specific receptors, and are therefore considered to be components of the innate immune system, express receptors which bind to the Fc region of antibodies. The Fc receptors thus enable these cells to bind antigens via interaction with antibodies specific for the antigens. The binding of an antibody with its antigen on the one hand, and with an Fc receptor on the other, are both high-affinity interactions: this is therefore a very efficient mechanism for targeting antigens to cells of the immune system.

An important aspect of antigen recognition by B cells is that these lymphocytes, and the antibodies they produce, bind to antigens in their natural or native form, i.e. as they occur as constituents of pathogens (**Figure 1**).

T lymphocytes

About 70% of human blood lymphocytes are T cells. The main functions of T lymphocytes are to exert effects on other cells, either regulating the activity of cells of the immune system or killing cells that are infected or malignant. Like B lymphocytes, T cells have surface antigen receptors, but there is no secreted form of these equivalent to antibodies. Furthermore, T cells cannot recognize antigens in their native forms, but only when they are presented on the surface of antigen-presenting cells (APCs). The antigen receptors of most T cells (αβ T cells) are composed of two polypeptides called α and β chains, and they interact with peptides derived from the degradation (processing) of foreign antigenic proteins. These peptides are bound to molecules of the major histocompatibility complex (MHC) on the surface of APCs (**Figure 1**). The interaction between the T-cell antigen receptors and the peptide–MHC complexes binds a T cell to the surface of an APC, thus targeting the T cell to exert effects on the APC. There are two types of MHC molecules, called class I and class II, which present antigen peptides to αβ T cells expressing the surface proteins CD8 or CD4, respectively. This is because CD8 binds to MHC class I and CD4 binds to MHC class II (**Figure 1**).

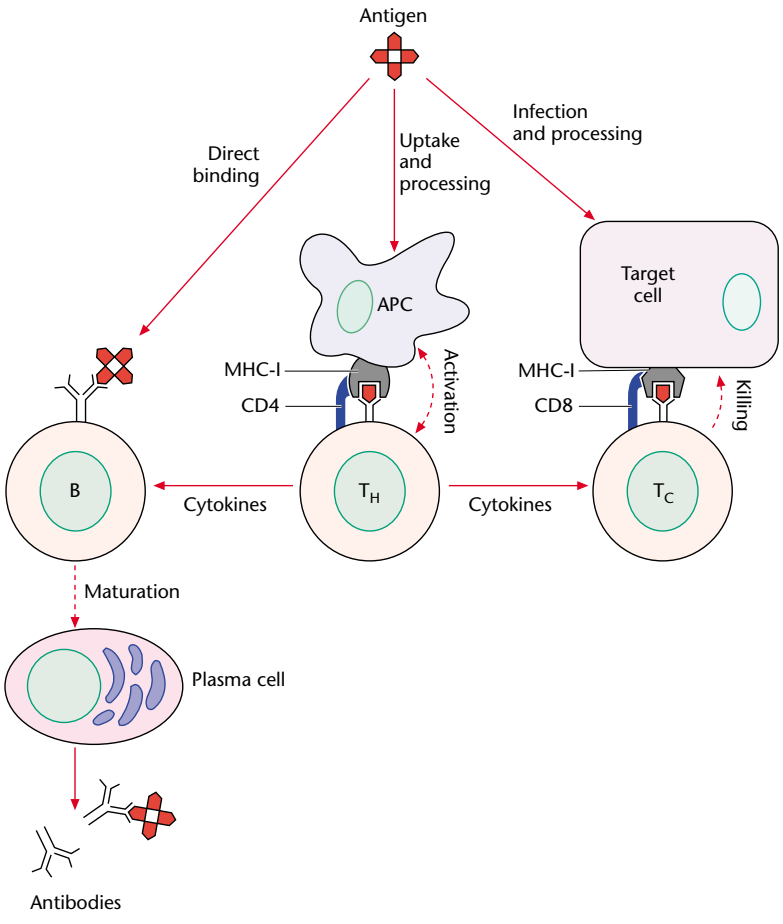

Figure 1 Lymphocytes: antigen recognition and its consequences. APC, antigen-presenting cell; MHC, major histocompatibility complex.

CD4+ T lymphocytes

The main function of CD4-expressing T cells is to help other cells of the immune system to mediate immune responses: for this reason they are called helper T (T_H) cells (**Figure 1**). For example, T_H cells help B cells to become activated and differentiate into plasma cells, or help macrophages to become more effective at killing bacteria. Macrophages and B cells, together with dendritic cells, are known as professional APCs because they normally express MHC class II molecules when activated, whereas most other cells of the body do not. This targets CD4+ T_H cells to interact with these cells, thereby giving the appropriate focusing of their activity. Indeed, the binding of T_H cells to professional APCs is a mutual interaction in which the APCs activate the T cells as well as vice versa.

The activities of T_H cells involve not only direct interactions between cell surface molecules, but also the effects of secreted regulatory proteins known as cytokines. Different T cells develop different profiles of cytokine production: T_H1 cells secrete cytokines (e.g. interleukin 2 and interferon γ) that mainly promote cell-mediated immunity by cytotoxic T cells and macrophages, whereas the cytokines produced by T_H2 cells (e.g. IL-4 and IL-10) primarily stimulate antibody production by B cells. Some cytokines also downregulate immune responses by suppressing the activity of cells of the immune system. For example, T_H1 and T_H2 cells are mutually inhibitory by virtue of the cytokines they produce, and some T lymphocytes (called T_H3 cells) produce transforming growth factor β, which is generally immunosuppressive.

CD8+ T lymphocytes

The main function of CD8-expressing T cells is to kill cells that have become infected or malignant: for this reason they are known as cytotoxic (T_C) cells (**Figure 1**). For example, in virally infected cells, some of the newly synthesized viral proteins are processed into peptides which associate with MHC class I molecules and are

presented on the cell surface. These cells then become targets for CD8+ T_C cells with receptors specific for the viral peptides. Once the T_C cells have bound to the infected cells, they have several mechanisms by which they can kill their targets. The T_C cells secrete proteins stored in granules in their cytoplasm. These include perforins, which form pores through the surface membranes of the target cells, and granzymes, which enter the target cells through the perforin pores to activate caspase enzymes involved in apoptosis. T_C cells also express a surface molecule called Fas ligand and a cytokine called tumour necrosis factor. These can induce apoptosis by binding to their respective receptors on target cells.

In contrast to the limited expression of MHC class II molecules, most cells normally express MHC class I molecules and are thus potential targets for T_C cells if they become infected or malignant.

γδ T lymphocytes

The antigen receptors of some T cells are not made up of α and β chains, but comprise alternative polypeptides called γ and δ. These γδ T cells constitute 10–15% of human blood T cells, but are abundant in epithelia of the gut, lungs and skin, where they appear to be important in immune responses to epithelial pathogens. Some mature in the thymus but others migrate directly from the bone marrow to the gut and mature there. The antigen receptors of γδ T cells show much more limited diversity than those of αβ T cells and do not recognize processed antigen peptides associated with conventional MHC class I and class II molecules: rather, they bind to other MHC class I-like molecules and nonprotein phosphorylated molecules expressed by cells undergoing stress, as may occur during infection. Indeed, some of the phosphorylated ligands recognized by γδ T cells may be expressed by bacteria themselves. When activated, γδ T cells secrete cytokines, particularly those that promote T_H2 types of responses.

Natural Killer Cells

Natural killer (NK) cells constitute up to 15% of human blood lymphocytes. Together with γδ T cells and about 50% of CD8+ T cells they are known as large granular lymphocytes because, compared with most T and B lymphocytes, they have more cytoplasm and contain prominent granules. In contrast to all T and B cells, NK cells do not express antigen-specific receptors and do not possess the adaptive property of memory cell development: they are therefore considered to form part of the innate immune system. However, like T_C lymphocytes, their main function is to kill infected cells and tumour cells using similar mechanisms to those of T_C cells to induce apoptosis of their targets.

Since they lack antigen receptors, NK cells do not recognize specific antigens on the surface of a target cell. Instead, they detect molecular changes in the surface of a cell which are indicative of that cell being abnormal and therefore a potential threat to the body. In particular, they kill cells with reduced expression of MHC class I molecules, as can result from viral infection or malignant transformation. NK cells express surface ligands for MHC class I known as killer inhibitory receptors (KIRs) because their binding to MHC class I on the surface of a potential target cell inhibits the cytotoxic activity of the NK cell. This prevents NK cells from killing normal tissue cells with normal levels of MHC class I expression. However, when they interact with infected or malignant cells with reduced expression of MHC class I the lack of KIR engagement allows activation of the cytotoxic mechanisms. A variety of NK cell surface molecules can be involved in the interactions with targets cells which lead to killing, including CD2, CD16, CD69 and lectins (sugar-binding proteins). In addition, NK cells bear Fc receptors for IgG, so that killing can result from interaction with antibodies specifically bound to antigens on a target cell surface: this is called antibody-dependent cellular cytotoxicity (ADCC).

Since they do not require activation by specific antigen in order to mediate their effects, NK cells are effective killers of infected cells during the early stages of a viral infection (thus demonstrating their 'natural' cytotoxicity) and help to limit the spread of the infection within the body until virus-specific T_C lymphocytes become active. Indeed, NK cells are activated by interferon α, which is produced by virally infected cells, and are themselves a source of interferon γ, which helps to promote cell-mediated immunity. All large granular lymphocytes (NK cells, γδ T cells and some CD8+ T cells) can be activated by the T_H1-derived cytokine interleukin 2 (IL-2) to exhibit enhanced antigen nonspecific cytotoxicity; these are called lymphokine-activated killer (LAK) cells.

Dendritic Cells

Dendritic cells are so called because, when they are mature, their cytoplasm extends into transient spiny dendrites and sheet-like veils. This provides a large surface area for their main function of antigen presentation to T lymphocytes. Indeed, they are the most potent APCs for T cells, expressing ten to a hundred times more antigen peptide–MHC complexes than the other professional APCs (B cells and monocyte/macrophages).

All dendritic cells are derived from bone marrow stem cells, but appear to be heterogeneous, with various precursors (including monocytes) differentiating into dendritic cells when stimulated by appropriate combinations of cytokines. Immature dendritic cells are found in tissues throughout the body (e.g. Langerhans cells in the

skin epidermis) and are very efficient at capturing and processing antigens: they can ingest particulate antigens (phagocytosis), engulf material in the surrounding fluid (macropinocytosis), and take up (by receptor-mediated endocytosis) sugar-bearing antigens which bind to surface lectins or antigen–antibody immune complexes which bind to Fc receptors. The internalized antigens are degraded into peptides and some of these associate with cytoplasmic MHC molecules followed by transportation to the cell surface for presentation.

The dendritic cells which have captured and processed antigen mature into potent APCs as a result of their interaction with antigen and stimulation by cytokines and certain microbial products (e.g. lipopolysaccharide). This strong T-cell stimulatory capacity of the mature dendritic cells is due not only to their high levels of antigen peptide–MHC, but also to their expression of numerous costimulatory adhesion molecules and cytokines. The antigen-laden dendritic cells migrate to secondary lymphoid tissues (lymph nodes and spleen) where they form clusters with T and B cells and stimulate antigen-specific immune responses: they present antigen peptides associated with both MHC class II and MHC class I molecules, and so can induce primary activation of both CD4+ T_H cells and CD8+ T_C cells, respectively.

Dendritic cells not only activate T cells specific for antigens of foreign pathogens, but also help to prevent T cell reactivity against the body's own components. If the body does not have this 'self-tolerance', autoimmune diseases can develop. In the thymus, T cell precursors which develop antigen receptors specific for self antigens are eliminated if they interact with thymic dendritic cells expressing these antigens, and similar interactions with mature self-reactive T cells in secondary lymphoid tissues may also help to maintain the ability of the immune system to discriminate between foreign and self components.

Follicular Dendritic Cells

Within the B cell-rich follicles of secondary lymphoid tissues there are cells with dendritic morphology known as follicular dendritic cells (FDCs). These are not related to the dendritic cells discussed above; they are probably of mesenchymal origin rather than bone marrow derived and they do not express MHC class II. The function of FDCs is to present antigens to B cells (rather than to T cells), thereby sustaining the viability, growth and differentiation of activated B cells. They express Fc receptors which enable them to bind immune complexes of antibodies bound to antigens. This surface binding of antigens is also facilitated by the expression of complement receptors on FDCs. Complement is the collective name for a number of proteins found in the blood and in tissue fluids which are activated in the course of immune responses and have a variety of immunological functions. These proteins can be activated either by antigen-bound antibodies or by direct interaction with microbes. Certain of the activated complement proteins (particularly C3b) bind to antigens and immune complexes and can therefore be involved in binding antigens to the surface of FDCs via the complement receptors. Thus, the antigens presented by FDCs to B cells are not processed by degradation into peptides, and are not bound to MHC molecules.

Following antigen recognition, activated B cells form germinal centres in the lymphoid follicles. The continued survival and maturation of these activated B cells is dependent on their interaction with antigens held on the surface of the FDCs within the germinal centres. The B cells which successfully do this are those whose receptors have the highest affinity for the antigen (possibly as a result of somatic mutation). The B cells which do not interact with the FDCs in this way die by apoptosis.

Monocytes and Macrophages

Monocytes, which constitute 5–10% of mononuclear leucocytes in the blood, differentiate into macrophages when they migrate into tissues. The main functions of macrophages are to phagocytose (i.e. engulf) and destroy particulate material and, by virtue of expressing MHC class II, to present antigens to T_H cells (discussed above).

The blood monocytes arise from myeloid progenitors in the bone marrow. Monocytes are larger than most lymphocytes and have a kidney-shaped nucleus: they possess azurophilic lysosomal granules containing lysozyme, acid hydrolases and myeloperoxidase. Macrophages can be resident in tissues for prolonged periods of time where they take on various morphologies, and are known by different names, depending on their tissues of residence, e.g. Kupffer cells in the liver, mesangial cells in the kidney and microglial cells in the brain.

Macrophages have a variety of surface receptors for binding particulate antigens such as bacteria; these include receptors for certain sugars (e.g. mannose) and for lipopolysaccharide (via interaction with LPS-binding protein). They also have Fc receptors and complement receptors enabling them to bind antigens which have been coated (i.e. opsonized) with IgG antibodies and C3b complement protein, respectively. In addition to the removal of microbes, macrophages are also important in the rapid clearance of tissue cells dying by apoptosis and, for example, have receptors for phosphatidylserine expressed on the outer surface of apoptotic cells.

The binding of particulate material to a macrophage triggers phagocytosis: the material is enveloped in cytoplasm, forming an intracellular vesicle called a phagosome. Lysosomes fuse with the phagosome so that their contents can participate in the destruction of the ingested material.

This destruction is mediated partly by reactive oxygen species (e.g. hydroxyl radicals and nitric oxide) generated by enzyme activity known as the oxidative or respiratory burst, and also by the digestive lysosomal enzymes.

The maximal activation of macrophages to mediate phagocytosis and killing, and also antigen presentation, is stimulated by cytokines, particularly interferon γ. Macrophages are themselves producers of cytokines and inflammatory mediators like prostaglandins and leucotrienes. They are also an important source of some complement proteins.

Neutrophils

Granulocytes, so named because of their prominent cytoplasmic granules, comprise the majority of white blood cells (60–70%). They are also known as polymorphonuclear leucocytes because of their multilobed nuclei and are larger than most mononuclear blood cells. Derived from myeloid progenitors in the bone marrow, granulocytes are released at a rate of seven million per minute, but are short-lived (2–3 days). They migrate into tissues, particularly to sites of infection where they are involved in the acute response.

Neutrophils account for 95% of granulocytes in the blood. Like macrophages, they contain azurophilic lysosomal granules which, in addition to myeloperoxidase, lysozyme and acid hydrolases, contain other antimicrobial proteins (e.g. defensins and serprocidins). They also possess secondary specific granules which contain the iron-binding protein lactoferrin as well as lytic enzymes.

The main function of neutrophils is the phagocytosis and intracellular digestion of particulate antigens (e.g. bacteria) essentially as described for macrophages. Thus, neutrophils express a similar range of receptors for binding their targets, including Fc receptors (20-fold more than macrophages) specific for IgG or IgA, and complement receptors for binding opsonized material. They also bring about destruction with reactive oxygen species and the antimicrobial enzymes and proteins. The vast number of neutrophils in the circulation means that they have a prominent role in the acute phase of the response to bacterial infection. They also produce some cytokines as well as prostaglandins and leucotrienes. In contrast to macrophages, neutrophils do not normally express MHC class II and so do not present antigens to T_H cells.

Eosinophils

The granulocytes whose granules stain with acidic dyes are called eosinophils. They comprise 2–5% of white blood cells and have bilobed nuclei. In contrast to the phagocytosis and intracellular digestion normally displayed by neutrophils, eosinophils secrete their granule contents for extracellular digestion of infectious pathogens which are too large to be engulfed (e.g. parasitic worms). Eosinophils have Fc receptors for IgG and IgE antibodies and for C3b, enabling them to bind to opsonized targets. They then secrete their antibiotic granule contents (including major basic protein and eosinophil cationic protein) and reactive oxygen species to bring about damage to the target.

Eosinophils also produce cytokines, prostaglandins and leucotrienes, and enzymes which can inhibit the inflammatory products of mast cells (e.g. histaminase and aryl sulfatase).

Basophils and Mast Cells

The main products of basophils and mast cells are mediators which promote inflammatory responses. Basophils (so called because their granules stain with basic dyes) are found in the circulation where they constitute less than 1% of white blood cells. Mast cells occur in tissues in two forms – connective tissue mast cells and mucosal mast cells. The latter are the most similar to basophils.

There are two main mechanisms for mast cell activation during the course of immune responses, e.g. at a site of infection. Mast cells have high-affinity Fc receptors for IgE and are coated with IgE antibodies which they adsorb from their surroundings. Specific binding of antigen to multiple IgE molecules so that they are crosslinked on the mast cell surface triggers activation. Mast cells can also be stimulated by small peptides called anaphylatoxins (C3a and C5a) produced during complement activation.

The activation of mast cells triggers their release of a wide range of inflammatory mediators; some are stored in cytoplasmic granules and released immediately upon activation (e.g. histamine, heparin and factors which attract neutrophils or eosinophils), whereas others are synthesized *de novo* and are released more slowly (leucotrienes, prostaglandins and platelet-activating factor). Mast cells can also produce various cytokines. The cumulative effect of all these inflammatory mediators (together with those from other cells) produced at a site of infection is to facilitate and encourage the movement of lymphocytes, monocytes, granulocytes and their products (e.g. antibodies and complement proteins) out of the bloodstream and into the underlying tissues where they can fight the infection.

Other Cells which Contribute to the Immune System

The appropriate regulation and functioning of cells of the immune system requires not only that they interact with

antigens and with each other, but also with other cells of the body. In this context, many cells of the body can contribute to the effective functioning of the immune system.

The non-nucleated cellular elements of blood, i.e. platelets and erythrocytes, have immunological effects in addition to their other functions. Platelets are essentially membrane-bound cellular fragments derived from megakaryocytes in the bone marrow. They contain granules which are an important source of inflammatory mediators (e.g. 5-hydroxytryptamine). They have surface adhesion molecules which enable them to bind to the walls of damaged blood vessels and contribute to the inflammatory response. Platelet-activating factor from activated granulocytes and macrophages can also stimulate their degranulation.

Erythrocytes play an important role in the clearance of antigen–antibody immune complexes from the circulation in humans and other primates. Following complement activation, C3b adheres to immune complexes which can then bind to complement receptors on the surface of erythrocytes. As the erythrocytes pass through the liver and spleen, the complexes are removed and degraded by macrophages. If immune complexes are not cleared from the bloodstream in this way they can become deposited in tissues (particularly the kidney), leading to tissue damage.

A variety of cells regulate the development, survival and migration of B and T lymphocytes. The development of B cells requires interactions with bone marrow stromal cells, and interactions of T-cell precursors with epithelial cells in the thymus promotes the maturation of those with receptors that will recognize foreign (rather than self) antigens. Many normal tissue cells throughout the body can be induced to express MHC class II molecules (particularly at sites of inflammation), enabling them to interact with T_H cells either to tolerize them or activate them, depending on the circumstances.

The endothelial cells which line blood vessels form both a barrier and the gateway between the blood and the tissues. Within most normal tissues the endothelium forms a tight barrier, preventing anything more than a trickle of white blood cells into the tissues. However, endothelial cells can be activated by certain cytokines and inflammatory mediators to express adhesion molecules to which leucocytes can bind, facilitating their passage through loosened intercellular junctions. This occurs at sites of inflammation (e.g. where the underlying tissues are infected), but is also a normal process within the postcapillary venules of lymph nodes, thus facilitating the passage of T and B cells from the blood into lymphoid tissues during their recirculation around the body.

The nervous and endocrine systems have important effects upon the immune system, and lymphocytes have receptors for a variety of neuropeptides and hormones. For example, corticosteroid hormones are potent suppressors of many immune responses.

Further Reading

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