Innate Immune System

Activation of the Innate Immune System

Neutrophils, eosinophils, basophils, macrophages/monocytes, dendritic cells, and NK cells are the cellular constituents of the innate immune system. These cells depend on a variety of soluble factors, such as serum and tissue proteins, to generate nonspecific immune responses. Of particular importance is the complement system, a group of plasma enzymes and regulatory proteins that are converted from inactive proenzymes to active enzymes in a controlled and systematic cascade.

Cells of the innate immune system sense infection, cellular damage, and threat to tissue integrity by means of a variety of receptors and respond with an activation program. They possess surface receptors for complement factors. They are activated by binding antibody molecules through immunoglobulin crystallizable fragment (Fc) receptors. Finally, they express pattern recognition receptors (PRRs) that are instrumental in recognizing microbial invasion. Beyond its response to soluble factors, the innate immune system is able to screen cells for intactness by surveying cell surface molecules. In principle, recognition of membrane molecules provides inhibitory signals for constitutively activated cells of the innate immune system. Loss of these membrane molecules on the tissue abrogates inhibition and allows the generation of protective effector functions .

Cellular Elements of the Innate Immune System

Monocytes and Macrophages

Monocytes circulate in the peripheral blood with a half-life of 1 to 3 days. Macrophages arise from monocytes that have migrated out of the circulation and have proliferated and differentiated in tissue. Tissue macrophages are

common in lymphoid organs, but they also are present in connective tissues, such as the perivascular space, and in the lining of serous cavities (pleura and peritoneum). Specialized macrophages include alveolar macrophages in the lung, Kupffer cells in the liver, osteoblasts in bone, microglia in the central nervous system, and type A synoviocytes in the synovial membrane.

Dendritic Cells/Langerhans Cells

Natural Killer Cells

The current paradigm holds that NK cells provide the first line of defense against viral infections and other intracellular pathogens while adaptive responses are generated. NK cells are sensitized by cytokines released from macrophages and dendritic cells. They function by secreting cytokines, mainly IFN-γ, which activate macrophages and other cells. They also are poised to kill virus-infected cells. NK cells induce apoptosis of the target cells by injecting pore-forming enzymes and granzymes. One of the interesting features of NK biology is the activation of these lymphocytes when MHC class I molecules on target cells are lost.

Neutrophils, Eosinophils, and Basophils

Neutrophils

Eosinophils

Basophils

Adaptive Immune System

The innate immune system recognizes structural patterns that are common in the microbial world, whereas the adaptive immune system is designed to respond to the entire continuum of antigens. This goal is achieved through two principal types of antigen recognition receptors: antibodies and T-cell receptors (TCRs). These receptors distinguish antigens through subtle changes in shape. The antigen recognition structures are complementary to the

shapes of the antigens and bind antigens noncovalently. Antibodies are expressed as cell surface receptors on B cells or are secreted. They recognize conformational structures, which are determinants formed by the tertiary configuration of proteins. In contrast, α/β TCRs fit specifically to epitopes formed by a small linear peptide embedded into MHC molecules on the surface of antigen-presenting cells.

Cellular Elements of the Adaptive Immune System

T Cells

T-Cell Development

T precursor cells derived from hematopoietic stem cells are seeded into the thymus, where all the subsequent stages of T-cell maturation occur . Pre-T cells express two enzymes, recombinase and terminal deoxynucleotidyl transferase, enabling them to recombine TCR genes. The β-chain of the TCR is rearranged first and is expressed together with pre-TCR α-chain.

B Lymphocytes

B-Cell Development

B cells are generated in the bone marrow. Supported by a specialized microenvironment of nonlymphoid stromal cells, lymphoid stem cells differentiate into distinctive B-lineage cells. Driven by chemokines (stromal cell–derived factor 1) and cytokines (IL-7), precursor B cells enter a process of tightly controlled sequential rearrangements of heavy-chain and light-chain immunoglobulin genes. On pre-B cells, the membrane μ-chain is associated with a surrogate light chain to form a pre-B-cell receptor (BCR). Signals provided through this receptor are believed to induce proliferation of a progeny that subsequently rearranges different light-chain gene segments.

The immune system faces a considerable challenge in its efforts to maintain tissue homeostasis in the intestinal mucosa. It is constantly confronted

with a large array of antigens, and has to prevent the dissemination and proliferation of potentially harmful agents while sparing the vital structures of the intestine from immune-mediated destruction. Complex interactions between the highly adapted effector cells and mechanisms of the innate and adaptive immune system generally prevent the luminal microflora from penetrating the intestinal mucosa and from spreading systemically.

Non-haematopoietic cells critically contribute to the maintenance of local tissue homeostasis in an antigen-rich environment by producing protective factors (e.g. production of mucus by goblet cells, or secretion of microbicidal defensins by Paneth cells) and also through interactions with the adaptive and innate immune system (such as the production of chemotactic factors that lead to the selective recruitment of immune cell subsets). The complexity of the regulatory mechanisms that control the local immune response to luminal antigens is also reflected in the observation that mutations in immunologically relevant genes often lead to the development of uncontrolled inflammatory reactions in the microbially colonized intestine of experimental animals.

Innate Immune Tolerance

(A) Complement System

1) Activation Of Complement

As an essential component of the innate immune system, complement is endowed with redundant, yet carefully controlled activation pathways. The molecular events that occur during activation not only are responsible for the pathology of complement-associated disease states, but also offer opportunities for the rational design of inhibitors. For simplicity, it is convenient to think of the different parts of the complement activation pathways as involving recognition, convertase/amplification, and effector mechanisms.

B) Innate Regulatory NKT Cells

The complexity of the immune system requires mechanisms, cellular and molecular, that coordinate early innate immune responses to those of late adaptive immune responses. One type of immune cell that is able to mediate this bridge between innate immunity and adaptive immunity is the invariant natural killer T (NKT) cell. In recent years, much research has been focused on describing the role of NKT cells in a variety of immune responses, from pathogen clearance, cancer immunity, to autoimmune regulation. In each of these immune conditions, NKT cells have been shown to play direct or indirect roles in the coordinating immune responses leading to downstream effector activation. In this review, we highlight our current understanding of NKT cell biology, and provide an overview of NKT cell antigen specificities and of the role of NKT cells in regulating immune responses.

Adaptive Immune tolerance

(A) Central tolerance

The first major event in the function of the immune system is the differentiation and the development of the so-called lymphocyte repertoire, which means the rising of a pool of T and B lymphocytes equipped with all possible antigen-specific receptors. These receptors in B cells are surface-bound immunoglobulins, which are capable of recognising antigen in its native form. Antigen-specific receptors in T cells are the already mentioned TCR, which interact with a peptide fragment of antigen when it is presented in the context of MHC.

(B) Peripheral tolerance

It is obvious that, despite the discovery of the promiscuous gene expression at thymic level, which can explain how immature T cells can encounter in the thymus even self peptides previously thought to be restricted to organs other than thymus, not all self-reactive T cells can be deleted through

the process of negative selection. Likewise, not all self antigens can be encountered in the bone marrow by immature B lymphocytes. At birth, therefore, many clones of autoreactive mature T and B cells are present at level of secondary lymphoid organs, where they represent a high potential risk for the development of autoimmune responses during the course of life. To avoid this possibility, other mechanisms are operating on autoreactive mature lymphocytes even in the periphery. Peripheral tolerance for mature B cell can occur under two main conditions. The first is when the B cell encounters the specific antigen in the absence of the specific Th cell.

Hepatic Tolerance

Fetomaternal Tolerance

A- Complement System Tolerance Disorders

The role of the innate immune response in autoimmune disease

Autoimmune diseases are multi-factorial processes involving dysreguiation of multiple components of the immune system including the adaptive and the innate immune system .

Innate immune cells usually recognize pathogen "patterns" by so-called pattern recognition receptors. Different Toll-like receptors specifically recognize bacterial 01 fungal cell wall components, bacterial flagellae 01 viral RNA Homologous recombination of T-cell or B-cell receptors of the adaptive immune system induces a high diversity of adaptive immune cell specificities. Since T- and B-cell receptors ate randomly rearranged, their repertoire likely includes receptors that recognize host antigens, also referred to as self- or auto-antigens. Clinically manifest autoimmune disease is usually prevented by distinct "quality control" processes. "Central tolerance" in the thymus serves as one of the most important processes.

Type I Diabetes Mellites

Psoriasis

Lupus erythematosus

Glomerulonephritis

Mixed Cryoglobulinemia

Lupus Nephritis

Arthus Reaction

Serum Sickness

Paroxysmal Nocturnal Hemoglobinuria

Hemolytic Transfusion Reactions

Myasthenia gravis

Multiple Sclerosis

Hereditary Angioedema

Septic Shock

Natural killer Cell Tolerance Disorders

1-Malignancy

B-Transplantation Rejection and Graft-versus-Host Disease

2) Adaptive Immune tolerance disorder

Allergy

Wegener granulomatosis

Aplastic Anemia

Hepatic tolerance disorder

Auto-Immune Liver Diseases and Their Overlap Syndromes

Feto-maternal Tolerance disorder