

Running Head: IMMUNE SYSTEM

Immune System Structure and Function

Mary W. Meagher

Department of Psychology

Texas A&M University

Address correspondence to: Mary Meagher  
Texas A&M University  
Department of Psychology  
College Station, TX 77843-4235  
E-mail: [M-Meagher@tamu.edu](mailto:M-Meagher@tamu.edu)  
Phone: 979-845-2564  
Fax: 979-845-4727

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## Immune System Structure and Function

The immune system is engaged in a constant surveillance of the body for pathogens or tumors. Whether disease develops depends on the virulence of the pathogen and the competence of the immune system. To prevent disease, the immune system must recognize, attack, and remember substances that threaten health, either foreign pathogens or mutations of the body's own cells. To do so, it must be able to distinguish self from non-self substances called *antigens* (meaning “antibody generators”). To efficiently eliminate antigens, the immune system must respond as quickly and as strongly as possible to kill abnormal cells or infectious agents. At the same time, it must be tightly regulated to avoid destroying healthy tissues. When immune regulation breaks down, excessive inflammation can cause collateral damage resulting in *autoimmune and allergic diseases*. Conversely, immunosuppression can result in increased susceptibility to infection, and malignant tumors can arise when there is unchecked growth of mutant cells.

### Components of the immune system

All of the cells of the immune system are derived from stem cells in the bone marrow. These cells give rise to two classes of progenitor cells: (1) *lymphoid progenitors* are precursors to antigen specific *T and B lymphocytes*, and (2) *myeloid progenitors* are the precursors for the nonspecific macrophages, monocytes, dendritic cells, mast cells, and granulocytes (neutrophils, eosinophils, basophils). *B-cells* remain in the bone marrow during development, selection, and maturation, whereas *T-cells* migrate to the thymus to mature. Once mature, T and B-cells emerge from these *primary immune organs* to reside in *secondary immune organs*, e.g., lymph nodes, spleen, tonsils, and lymphoid mucosa. T and B-cells circulate from lymphoid organs to the tissues through lymphatic and blood vessels, monitoring sites where pathogens are likely to invade the body (airways, gastrointestinal tract, reproductive tract, skin). Pathogens are normally taken up by *antigen-presenting cells* (macrophages and dendritic cells), which process and transport the antigen to secondary lymphoid organs where they induce T and B-cell responses. *Macrophages* are widely distributed throughout the body where they act as a first line of defense

to engulf and digest antigens, a process known as *phagocytosis*. They are derived from circulating precursor cells known as *monocytes*, which differentiate into macrophages once they enter tissues. Immature *dendritic cells* also circulate in the blood until they migrate into the tissues and mature after ingesting pathogen. Once mature, dendritic cells migrate to the lymph nodes to present antigen. *Mast cells* also differentiate in the tissues where they are located near small blood vessels and act to alter vascular permeability during allergic reactions. Neutrophils, eosinophils, and basophils are collectively known as *granulocytes*. They normally circulate in the blood until they are recruited to sites of infection and inflammation. Neutrophils play an important role in controlling bacterial infections, whereas eosinophils and basophils are involved in parasitic infections and allergic inflammation.

### **Functions of the immune system**

The functions of the immune system can be divided into two systems: (1) *innate* or nonspecific immunity, and (2) *specific* or adaptive immunity. These interacting systems differ in terms of the timing and specificity of their responses. Innate immunity provides an immediate but relatively nonspecific response to contain pathogens at the site of entry into the body. Innate immune defenses include inflammatory and acute phase responses, as well as the anatomical and chemical barriers provided by the skin and mucous membranes. Specific immunity is characterized by antigen-specificity through T and B lymphocytes. It also exhibits immunological memory, where heightened responses occur upon subsequent exposure to the same antigen, but this is not an immediate response. Although specific immunity is more selective and adaptive than innate immunity, it is a slow and complex process that occurs over several days to weeks. Conversely, innate immunity provides an immediate front line response, but it lacks memory and can damage healthy tissue due to its nonspecific nature.

### **Innate Immunity**

*Inflammation.* Inflammation is a local response designed to limit pathogen invasion and tissue damage. Phagocytes such as macrophages and neutrophils play a central role in the inflammatory response. They recognize foreign invaders through nonspecific receptors that

identify common features of pathogens. Because a large pool of phagocytic cells is readily available, inflammatory responses can be observed within 1-2 hours after infection. During this time, macrophages use several mechanisms to contain infection. First, they release toxic enzymes and ingest the invading cells. Activated macrophages also synthesize and release nitric oxide, a gas that interferes with the proliferation of bacteria and other pathogens. In addition, activated macrophages release substances called *cytokines*, which are chemical messengers secreted by one cell that communicate with other cells. Cytokines act locally to facilitate the inflammatory response and to attract other immune cells that promote healing at the site of infection or injury. For example, neutrophils, which normally flow freely in the blood stream, are recruited out of the circulation to the site of infection by cytokines such as interleukin-1 (IL-1) that are released by activated macrophages. A similar mechanism is used to recruit all *leukocytes* (white blood cells, including monocytes, granulocytes, and lymphocytes) to the site of infection or inflammation.

*Natural killer cells.* Natural killer cells (NK cells) are nonspecific lymphocytes that specialize in destroying tumor cells and virus-infected cells. Although they lack specific antigen receptors, they are able to recognize and kill some abnormal cells. NK cells secrete *perforins*, chemical bullets that blow holes in the pathogen's cell membrane allowing *granzymes* to enter the cell. Granzymes signal the target cell to commit suicide, a process known as *apoptosis*.

*Acute Phase Response.* Whereas inflammation begins as a local response designed to contain infection, a systemic reaction known as the *acute phase response* or *sickness syndrome* will occur if the infection spreads to other parts of the body. This response is triggered when high concentrations of inflammatory cytokines (e.g., tumor necrosis factor alpha, IL-1, and IL-6) enter the circulation to initiate a series of physiological and behavioral changes that help fight infection and promote healing. The acute phase response involves the release of proteins by the liver that migrate to the site of infection. Interestingly, some of these acute phase proteins act like nonspecific antibodies that bind a broad range of pathogens. Other physiological changes include fever, increased slow wave sleep, and increased leukocyte production and circulation.

Behavioral changes are also observed during the acute phase response, including decreased feeding, physical activity, exploration, social interaction, sexual activity, and aggression. Other psychological changes include increased pain sensitivity, depressed mood, and memory impairments. The highly conserved nature of these sickness behaviors, which are even observed in invertebrates, suggests that they evolved to help fight infection and enhance survival. Indeed, recent research indicates that sickness syndrome is an *adaptive motivational state* coordinated by the brain rather than a collection of reflexive responses reflecting the pathological consequences of infection or injury. Finally, activation of the *hypothalamic-pituitary adrenal (HPA) axis* is part of the acute phase response. Cytokines released during infection activate the HPA-axis to release *glucocorticoids*, hormones that help to mobilize energy and decrease inflammation. The latter negative feedback mechanism acts to counterregulate the inflammatory cytokines to prevent damage to normal tissues. However, when HPA-axis activity is blunted, excessive inflammation can result in immunopathology and contribute to the development of autoimmune diseases.

### **Specific Immunity.**

T and B cells use antigen-specific receptors to recognize and destroy antigens. To recognize antigen, part of the antigen must be presented to T-cells by an *antigen presenting cell* (APC), such as macrophages and dendritic cells. After engulfing and processing the antigen, the APC displays specific parts of the antigen on its surface. The T-cell interacts with an *antigenic site* on the displayed piece of antigen. T-cells have receptors that allow them to recognize and bind to specific antigenic sites. Thus, a large repertoire of T-cell receptors must be produced to adequately cover the large range of pathogens that will be encountered over the life span. When a T-cell receptor recognizes an antigenic site, it triggers *proliferation* and *differentiation* processes which normally occur in the lymphoid tissues. The T-cell rapidly divides to yield an army of T-cells with antigen-specific receptors that perform different tasks. Two classes of T-cells, *helper* and *cytotoxic T-cells*, are distinguished by CD4+ and CD8+ molecules on their surface, respectively. Both types of T-cells act to contain intracellular pathogens, but they also

perform distinct tasks. T-helper cells coordinate the immune response by assisting in antigen recognition and by secreting cytokines that activate other T and B-cells to increase their numbers. Cytotoxic T-cells are able to kill virus-infected cells or tumor cells and thus play a major role in antiviral and antitumor activity. Another class of T-cells, known as *suppressive T-cells*, can actively inhibit the actions of other T-cells through the secretion of suppressive cytokines. In the case of B-cells, they differentiate into plasma cells that secrete antibody. This process is normally triggered by antigen binding and helper T-cell activity. These plasma cells rapidly divide and secrete *antibodies*, immunoglobulin molecules that act as receptors for antigen. These are soluble molecules that circulate in the blood where they can inactivate antigen through binding or mark it to be destroyed.

Thus far we have described the *primary immune response* that is initiated when the immune system does not have prior experience with the antigen. During the primary response, a subset of lymphocytes differentiates into *memory T and B-cells* and remain in circulation for many years to provide immunity from diseases. Upon exposure to the antigen, memory T and B-cells respond quickly to eliminate the antigen, a process known as the *secondary immune response*.

### **Immune-related diseases**

The importance of the immune system is illustrated by immunodeficiency and autoimmune diseases. Persistent infection of the immune system by *human immunodeficiency virus* (HIV) leads to acquired immune deficiency syndrome, AIDS. HIV evades detection by hiding in immune cells. It destroys helper T-cells through its direct cytotoxic effects and by triggering cytotoxic T-cells. When helper T-cell counts plummet, susceptibility to opportunistic infections increase, leading to AIDS and eventual death. In *autoimmune diseases*, normal immune responses are directed against a self-antigen. For example, T-cells may lose their ability to distinguish between self and non-self due to the development of *autoreactive receptors* that bind self-antigen. Such self-reactive T-cells attack healthy tissues of the body causing diseases such as multiple sclerosis, type-I diabetes, Lupus, and rheumatoid arthritis. Other work suggests

that suppressor T-cells may lose their ability suppress the actions of cytotoxic T cells in autoimmune disease. By understanding the mechanisms mediating these diseases, research may lead to the development of innovative strategies for disease prevention and treatment.

### References

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