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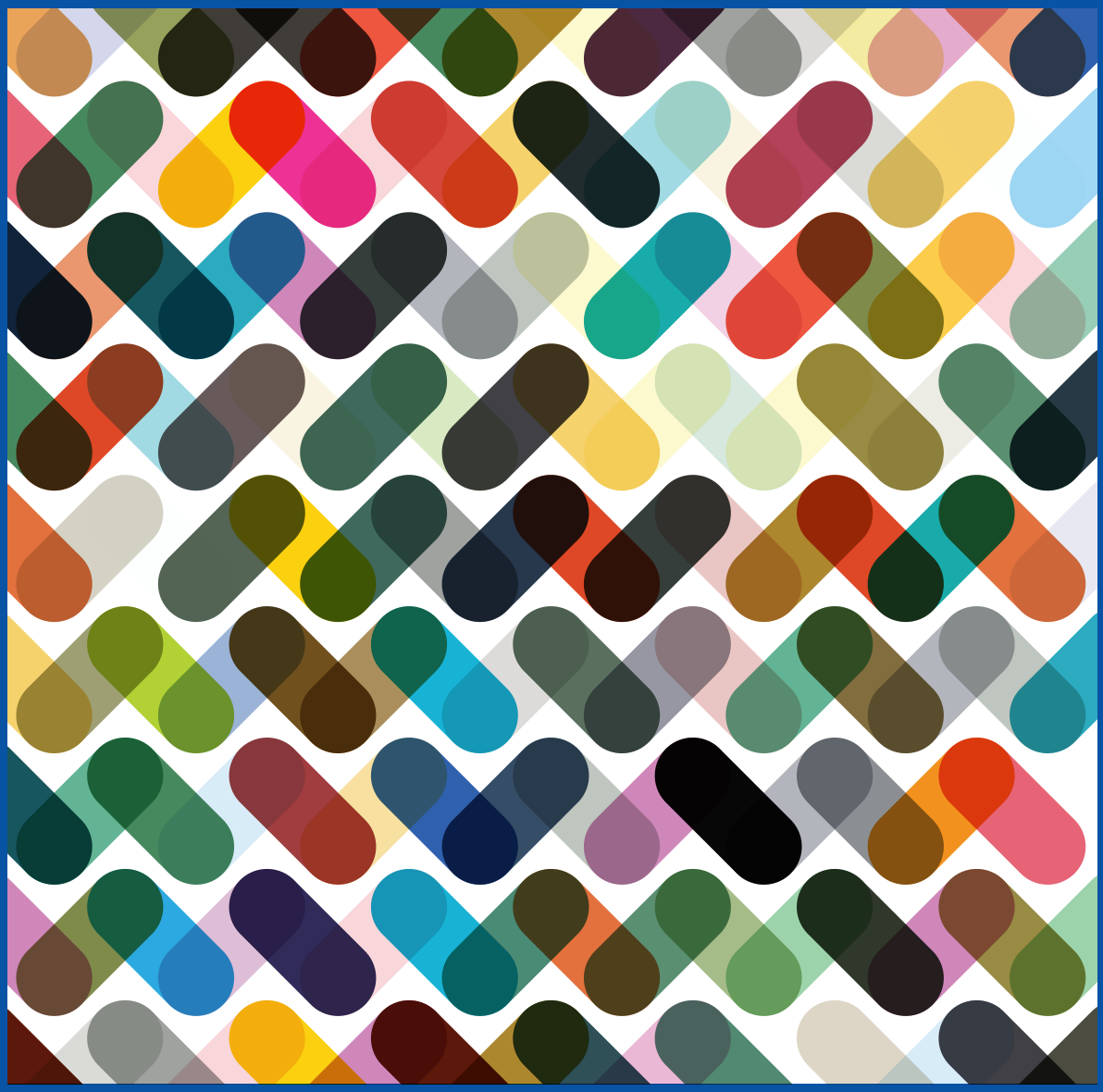


Chapter 5

Immunology

By Bruce Parker and Sarah Scott

Without an effective immune system, a human cannot survive. Pathogens, such as bacteria and viruses, constantly attempt to invade and attack a human host. What stands between health and disease is our immune system. The science of immunology is the study of the elegant and complex systems within humans and other mammalian species whose mission is to keep the host healthy.

The goal of this chapter is to provide a trial lawyer with a general understanding of human immunology. Immune system dysfunction, allegedly caused by drugs and devices, has been the injury in some mass tort litigation. In addition, while not the injury itself, immune system response to certain drugs and devices is an important element in the pathophysiologic explanation of some alleged injuries; consequently, understanding the immune system is important for counsel defending.

Because this is an overview, there are multiple layers of detail that will not be addressed, and thus, the chapter cannot be totally complete. For additional detail, the reader is referred to the major text material identified at the end of this chapter.

Overview of the Immune System

Humans (the "host") have physical barriers that prevent external threats from entering them. The primary physical barrier is the skin which prevents most pathogens from entering the body. Sweat is another external defense mechanism. Pathogens encountering sweat are killed by the acidity of sweat.

When the physical barriers are breached, the immune system seeks to protect the host. It is helpful to view the immune system as having two separate arms that, while capable of working independently, can and must work together. The two arms are the (1) "innate" and the (2) "adaptive" immune systems.

The purpose of both the innate and adaptive arms is to destroy that which is foreign to the host and capable of causing harm. To accomplish this, the immune system must be able to distinguish an external threat from the host's cells. If the immune system attacks the host for a sustained period of time, the result is the development of an autoimmune disease. When explaining how the innate and adaptive systems function, we will comment on how the immune system is able to differentiate between the host and pathogens.

Definition

Before discussing the roles that the innate and adaptive immune systems play in the host's defense, we will define some of the general terminology that will be used. Terms specific to either arm of the immune system will be defined in the discussion of that arm.

Pathogens

Pathogens are foreign organisms that can harm the host. Bacteria, viruses, parasites, and fungi are all pathogens.

Antigens

Antigens are substances that can physically bind to receptors (also called "determinants") on cells that are part of the innate and adaptive immune systems. An antigen fits into receptors on cells of the adaptive immune system in a way that is similar to how a unique key is only able to fit into a one lock. The

antigenic "keys" on an antigen are called "epitopes." Antigens that are capable of provoking an allergic response by inducing the synthesis of IgE are called allergens.

Immunogens

Immunogens are antigens that, after binding to an immune cell, induce an immune response. All immunogens are antigens but not all antigens are immunogenic. Pathogens are by definition immunogenic. In this chapter, we will use the term "immunogen" to distinguish between immunogenic and non-immunogenic antigens.

Leukocytes

Leukocytes are white blood cells. Both the innate and adaptive arms of the immune system consist primarily of leukocytes. There are many different types of leukocytes; Figure 1 illustrates the immune system leukocyte "family tree":

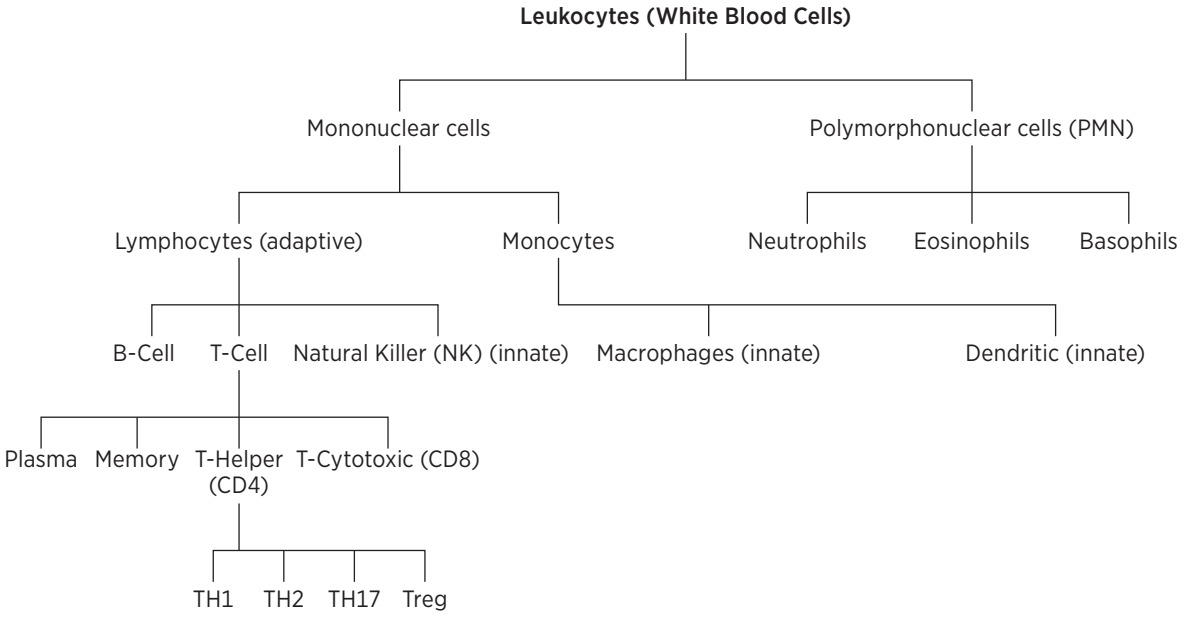
Innate Immune Response

The Innate Immune Response to Pathogens/Immunogens

The term "innate" refers to a quality with which one is born. The innate immune system is the arm of immune system comprised of leukocytes that are immediately available to perform their immunogen-fighting functions when a pathogen bypasses the host's physical barriers. The innate immune system contains the "first responders" against infection, which protect the host against pathogens during the first few days of an infection. Though these innate immune cells are immediately available and active, they do not retain a "memory" of an immunogen after they eliminate it, which is a distinguishing feature between these leukocytes and those in the adaptive immune system.

The "first responder" cells in the innate system are polymorphonuclear ("PMN") cells. This family of cells contains granules that are released during a response to a pathogen. A PMN cellular structure differs from a mononuclear cell which contains a single nucleus. The PMN family includes neutrophils, basophils, and eosinophils. While each of these cell types have slightly different functions, they all are capable of releasing substances into a pathogen that are toxic to it. PMN cells also ingest and digest pathogens in a process called phagocytosis. Finally, they recruit other immune cells to help fight the invading pathogens. PMNs live for only a couple days.

Monocytes are a subset of mononuclear leukocytes. Monocytes are part of the innate immune system. Monocytes are the largest leukocytes and are produced in the bone marrow. Once developed, they circulate in the bloodstream before moving into the host's tissues where they search for pathogens.



When monocytes are alerted to the presence of pathogens from cytokines released by other leukocyte cells, they enter the reticuloendothelial system ("RES") where they mature into macrophages. Macrophages have several functions. One is to ingest pathogens and present to its surface fragments of the pathogen, along with a molecule called the Major Histocompatibility Complex ("MHC") (*see* "Adaptive Immune Response: Cell Mediated Immune Response," *infra*). Once presented to the surface of the macrophage, the epitopes on the antigen bind to receptors on T cells that are called determinants. As discussed in "Adaptive Immune Response: Overview," *infra*, T and B cells are the primary cells involved in the adaptive immune response. When macrophages perform this function, they are called "Antigen Presenting Cells" ("APC"). A second function of macrophages is to signal B and T cells to the pathogens' location. Thirdly, macrophages remove dead or dying host tissue so that new cells can replace the dead tissue. Macrophages are long-lived cells. Unlike the specific binding characteristic of cells in the adaptive immune system, cells of the innate system, including macrophages, non-specifically bind to all antigens.

Dendritic cells are APC cells and, like macrophages, dendritic cells bind to epitopes on immunogens. Also, like macrophages, they ingest, digest, and present antigenic fragments along with the appropriate MHC molecule to its surface to allow for binding to a T cell.

Macrophages and dendritic cells are able to recognize what is foreign from what is self and thereby destroy immunogens while leaving the host's cells unmolested through a process of recognizing molecular patterns on a pathogen's surface. Pathogens have structures on their surface that are called "pathogen-associated molecular patterns" ("PAMPs"). PAMPs are specific molecular patterns that are common to groups of related immunogens. PAMPs are composed of molecules that are not found on human cells. The leukocytes involved in the innate immune response detect the PAMPs through receptors on their surfaces called "pattern recognition receptors" ("PRRs"). When the PPRs recognize a PAMP, they both attack the pathogen and trigger (through biochemical signals) cells of the adaptive immune system. Thus, cells of the innate immune system respond immediately to immunogens and assist in the later, more specific, and sustained response by the host's adaptive immune response.

Natural killer ("NK") leukocytes are another line of defense in the innate immune system. They are activated by, among other things, the cytokines emitted by macrophages. NK cells emit proteins that are toxic to pathogens. Instead of ingesting (phagocytizing) an immunogen, NK cells release their toxic payload directly into an immunogen that causes it to die. NK cells determine whether a cell is foreign based upon whether the cell is expressing an MHC protein. If it does, then the NK cell recognizes it as part of the host and will not kill it. If the pathogen does not express an MHC protein, then the NK cell will attack it.

The innate immune response also includes the release of soluble proteins that are collectedly referred to "complement." Complement proteins are made by the liver and circulate in the blood in inactive form. When the appropriate signal is generated by the innate system, many different subtypes of complement (each with different biological functions), are released into the blood. Some complement proteins are directly toxic to immunogens, while others function by loosening the walls of blood vessels, which enables circulating immune system cells to leave the vasculature and to enter adjacent tissue. There is an ordered process through which different components of the complement system are activated to perform different functions. The process of complement responding to immunogenic attack is referred to as the "complement cascade." Some of the complement proteins bind to immunogens, making them more attractive to be phagocytized (eaten) by innate immune cells. When complement performs this function, the process is referred to as opsonization.

The immune process that has just been described results in inflammation. The symptoms of inflammation are redness, tenderness, swelling, and heat. These symptoms are caused by components of the innate immune system responding acutely to remove immunogens from the host. If inflammation is not stopped once an immune response is no longer needed. it becomes chronic. Chronic inflammation can injure the host. This will be explained more fully in "Autoimmune Disease," *infra*, which addresses autoimmunity.

The Innate Immune Response to Foreign Objects

Thus far we have discussed how the innate immune system kills pathogens. What happens however when the invader is not a bacteria, virus, fungus, or parasite? For example, what happens when an object like a splinter or a medical device enters the host and cannot be eaten? When a splinter enters the skin, it damages the tissue that has been pierced by the splinter. The innate system responds in an effort to renew the dead or dying host cells. The "first responders" then recruit cells that release fibrin (collagen) around the invader. The fibrin cocoon that is created around the splinter walls it off from neighboring host cells. Once the foreign object has been isolated, the inflammatory response is shut down and the symptoms subside.

Adaptive Immune Response

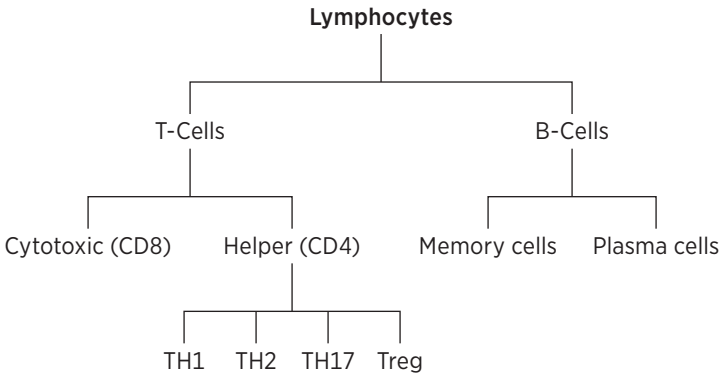
Overview

The adaptive immune response is a more intense and specialized response to an immunogen than is the innate response. Two primary attributes of the adaptive immune response are specificity and memory. Within the adaptive immune response, there are two arms. One is the humeral response that is discussed in "The Humeral Response," *infra*. It is primarily a B cell and antibody response. The second arm of the adaptive system is the cell mediated response discussed in "Cell Mediated Immune Response," *infra*. The cell mediated response is largely driven by activated T cells.

The main cells that constitute the adaptive immune system are B cells and T cells. While B and T cells have separate functions, to a great extent they are functionally dependent on each other. B cells are lymphocytes (a subset of leukocytes) that are responsible for developing protein antibodies called immunoglobins ("Ig"). A chart depicting the major subsets of lymphocytes appears below.

B cells develop and mature in the bone marrow. As B cells develop, they acquire the surface receptors necessary to perform their functions. It is during cellular development within the bone marrow that the host selectively kills a developing B cells that are not capable of differentiating what is foreign from that which is part of the host. After being released from the bone marrow, B cells will circulate in blood until they enter the secondary lymphatic organs: the spleen and lymph nodes. B cells, upon encountering an immunogen in the lymphatic system will mature into plasma cells. This maturation allows the B cell to produce Ig. This process is discussed more fully in the next section.

T cells are derived from stem cells in the bone marrow. As they mature, they leave the bone marrow and travel to the thymus where they complete their maturation. They eventually leave the thymus to begin functioning as a component of the adaptive immune system. While developing in the thymus, T cells that lack the ability to differentiate self from foreign are destroyed. Only those T cells that have the surface receptors that allow them to differentiate foreign antigens from self-antigens are permitted to leave the thymus. Specificity refers to the fact that each mature B or T cell will respond only to an immunogen that has a unique "key" (epitope) specific for the particular determinant (lock) on the B and T cells. Memory refers to the ability of B and T cells that have responded to an immunogen to remember having seen that immunogen and to live their remaining lives (and their progeny) looking for the same immunogen. If a re-encounter occurs,



the "memory" B and T cells can mount a quicker and more aggressive response. This is the principle behind vaccinations which is discussed in "Autoimmune Disease," *infra*.

While the innate and adaptive responses act independently to some extent, they are also dependent on each other. The interrelationship of both systems is depicted below.

The Humeral Response

The humeral immune response is primarily, but not exclusively, a B cell response. B cells have three primary functions. They directly bind to an antigen that has epitopes, which bind specifically to surface determinants on a B cell. They also phagocytize antigens, like macrophages and dendritic cells, and they present fragments combined to an MHC molecule on its surface to await "presentation" to a T cell. Finally, once sensitized to an immunogen, B cells will produce Ig that will bind to that specific immunogen and facilitate its destruction.

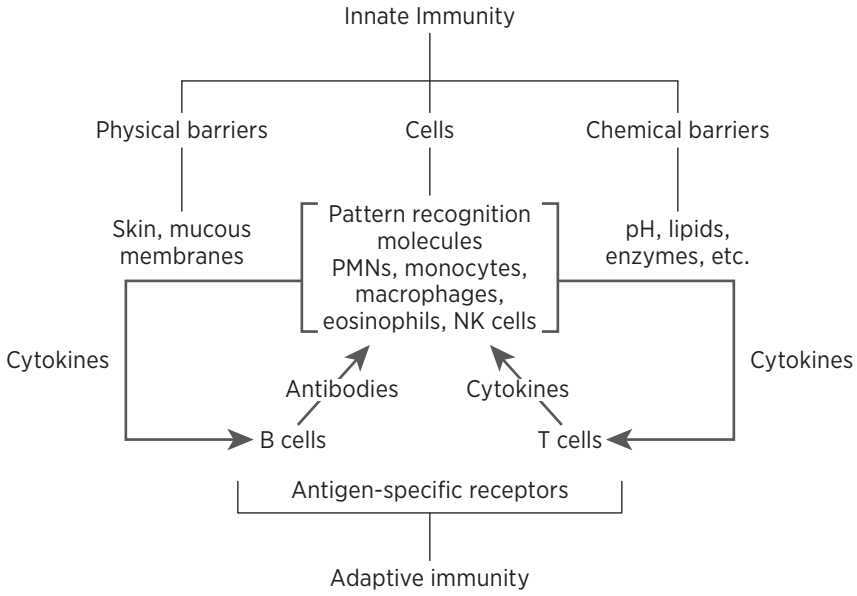
B cells have numerous surface receptors that have different functionalities. Naïve B cells (one that has not been immunologically sensitized) express on their surface two different types of Ig molecules (IgM and IgD) that both share the same binding specificity. These Ig receptors allow B cells to bind directly to an antigen.

B cells that have been immunologically sensitized undergo further maturation and develop into plasma cells. Some plasma cells are long lived and have the functional ability to produce antibodies for a specific immunogen.

There are five classes of Ig (IgM, IgG, IgD, IgE, and IgA). Each Ig has different biologic properties. Depending on the nature of the immunogen, the B cell will release one or more of its Ig classes. In addition to having different biologic purposes, each Ig class is released by plasma cells at different times, reaching peak concentration in the blood at different times. After responding to an infection, the plasma cells will migrate to the bone marrow where they continue to make and release Ig into the circulation as needed.

In addition to functioning as a surface receptor on B cells, IgM is the first Ig produced by plasma cells following sensitization to an immunogen. The half-life of IgM is approximately five days. IgM is relatively unimportant in terms of neutralizing toxins, but it is extremely effective at triggering the complement cascade upon binding to an immunogen.

IgG is produced after IgM. Like all Ig, IgG responds solely to extracellular immunogens, like bacteria. Ig are ineffective against viruses once they have entered a cell; however, Ig does help to neutralize a virus before it enters a cell. IgE primarily



Taken from "Immunology, A Short Course," p. 33 (7th ed. 2015).

responds to invading worms and is the class of Ig that are responsible for immediate allergic reactions. The role of IgA is less well understood, but it is important against pathogens encountered in the mucosal barrier.

Igs help fight pathogens in several ways. They can bind to bacteria before it enters a host cell and prevent the bacteria from releasing toxins. By coating the immunogen, it makes the immunogen a target for innate cells like macrophages and neutrophils to attack. Finally, certain types of Igs help trigger B cells to release complement.

Following eradication of the immunogen, most activated B cells will die except for a subset that mature into memory B cells. Their function is to wait for another encounter with the immunogen.

As previously mentioned, there is a dependency between B cells and T cells. One example of this includes antigens to which B cells will bind but need a co-stimulatory signal from T cells to allow the B cells to produce Ig. Such antigens are referred to as a TD antigens ("T cell Dependent"). Those antigens that can stimulate B cells to produce Ig without the assistance of a T cell are referred to as Thymus Independent ("TI") antigens.

Cell Mediated Immune Response

A cell-mediated response is largely driven by T cells. Unlike B cells, T cells do not bind directly to immunogens. In addition, unlike B cells, T cells can bind only to protein immunogens. In order for a T cell to respond, an APC must digest the antigen and present, on its surface, fragments of the degraded immunogen containing its epitopes coupled with an MHC molecule.

There are two genetically different types of the MHC (MHC I and II). Each serves a different role in activating T cells. MHC I will bind to cells that have surface makers that are labelled "$CD8^+$." Other T cells have different surface markers and have different properties. $CD8^+$ T cells are cytotoxic cells that respond when an immunogen, like a virus, is replicating intracellularly. MHC II will bind to another type of T cell that has a surface marker labelled "$CD4^+$". These are called "helper" T cells because they help stimulate B cells to make antibodies in response to an immunogen that is circulating extracellularly. There are also different subsets of CD4+ and CD8+ T cells that respond effectively to different types of immunogens, such as viruses, fungi, or extracellular bacteria. T cells that bind to a peptide/MHC complex will not become stimulated and generate an immune response (to "self" proteins) unless it receives a second or a "co-stimulatory" signal from the APC. This second signal alerts the T cell that the peptide being presented is foreign.

T cells respond to both exogenous and endogenous pathogens. An exogenous pathogen is one that enters the host and is thus foreign to the host. An endogenous antigen is a product that has been produced by a virus or bacteria that has invaded the host. The protein products released by bacteria and viruses are foreign despite having been produced within the host.

An APC that is expressing a peptide on its surface in combination with an MHC II molecule will bind to a $CD4^+$ receptor on a T cell. If the co-stimulatory signal is received, the $CD4^+$ cell differentiates into either a TH_1, TH_2, TH_{17} or Treg cell. Each of these subclasses perform different functions. For example, TH_1 are cells that promote a cell mediated cytotoxic response, similar to $CD8^+$ T cells.

TH_1 cells develop primarily in response to intracellular pathogens (bacteria and viruses). TH_1 cells release cytokines that attract NK cells, macrophages and $CD8^+$ cells. These cells kill the cells infected with the bacteria or virus.

TH_{17} cells secrete chemicals (called cytokines) that help promote an inflammatory response. T reg cells suppress the development of TH_1, TH_2 and TH_{17} cells and in doing so, helps to turn off the adaptive immune response when it is no longer needed. Which subset develops is largely dependent on the nature of the cytokines released by innate immune cells that have already responded to the pathogen.

$CD4^+$ cells can also differentiate into TH_2 cells. Cytokines released by TH_2 cells cause B cells to switch Ig production to IgE and certain subclasses of IgG. This is an effective defense against extracellular antigens but can produce injury to the host when the response is directed against allergens.

If the peptide is presented on the APC surface coupled with an MHC I molecule, the complex will bind to surface receptors on a $CD8^+$ T cell. When a bacteria or virus enters the body, it will eventually pass into the lymphatic circulation and eventually

get digested by an APC in the lymph node. Within the lymph node, an APC will present the antigen to a T cell along with MHC I. If a second signal is given, the $CD8^+$ T cell is activated. Once activated the $CD8^+$ T cell will attach to the target cell (infected by a pathogen) and kill it.

Once the pathogen has been neutralized, the large number of activated $CD4^+$ and $CD8^+$ T will no longer be needed. These cells are directed to die through activation of internal signaling. However as is the case with B cells, a small subset of T cells survive as memory cells. These cells can live for years and spend their lives looking for the same immunogen that led to their creation.

Antibiotics and the Immune Response

Broadly defined, an antimicrobial is a chemical designed to kill microorganisms. Antiseptics, disinfectants, and antibiotics are all antimicrobials. An antibiotic is a chemical that is targeted to kill bacteria, which is just one type of a microbe. An antibiotic kills a bacterium by either preventing it from reproducing or destroying its cell wall. For example, penicillin kills a bacterium by preventing it from developing its protective cell wall. Other antibiotics can breach an existing cell wall causing the bacterium to burst from internal pressure. Still others, such as erythromycin, kill bacteria by preventing the ribosomes within them from producing proteins that are necessary for their survival. Others, such as ciprofloxacin, kill bacteria by causing the DNA strands within them to break and prevents them from repairing the broken DNA. Without DNA, the bacteria cannot survive.

Unlike the adaptive immune response, antibiotics respond nonspecifically to bacteria. Thus, antibiotics will attack even friendly bacteria, including essential bacteria for normal gastrointestinal functioning that reside in the intestinal tract. Bacteria also become resistant to antibiotics over time as they evolve. For this reason, antibiotics must be used judiciously in clinical practice.

Bacteria have a nucleus which is the target of certain antibiotics. However, a virus does not have a nucleus and thus there is nothing for the antibiotic to attack. Viruses do not perform biological processes similar to those performed by bacteria. In addition, viruses do not have cell walls and thus antibiotics like penicillin are ineffective against viruses.

Vaccines and the Immune Response

The intent of vaccines is to interact with a host's immune system and thereby boost immunity to a given microbe.

Vaccines are designed to present microbe-specific immunogens to the host, thereby eliciting an immune response to that microbe, and ultimately preventing a full-blown infection by that microbe in the host. For example, the whooping cough vaccine is designed to create an immune response to a bacterial microbe, in order to prevent the development of the distinctive cough characteristic of whooping cough.

There are several different types of vaccines that achieve these goals in different ways. This chapter will discuss four main types of vaccines: (1) live, attenuated vaccines; (2) inactivated vaccines; (3) recombinant protein subunit vaccines; and (4) nucleic acid vaccines. Importantly, the vaccine type does not indicate whether it triggers a mainly humoral or a mainly cell mediated immune response. For example, the yellow fever vaccine is an attenuated, live virus vaccine. The tuberculosis vaccine is a live, attenuated bovine bacteria strain. However, the yellow fever vaccine primarily boosts the host's humoral immunity to yellow fever virus, while the tuberculosis vaccine primarily boosts the hos''s cell mediated immunity to tuberculosis bacteria.

Live, Attenuated Vaccine

Live microbe vaccines are basically significantly weakened versions of a microbe. They are created by taking a strain of a microbe and then "passaging" it so that the microbe does not replicate as well and so it becomes less virulent (*i.e.*, less effective at causing disease). Passaging occurs by growing the microbe in different environments that might impede some of its replicating or virulence capabilities. When this is done, the microbe has become "attenuated," or less virulent and less able to replicate in the host. The key is to create a vaccine that will be strong enough to cause an immune response in the host, thereby creating a memory of that immunogen, while not so strong that the virus is able to replicate in the host sufficiently to cause the disease it aims to prevent. These vaccines have historically been preferred, as they generally result in an effective and long-lasting vaccine.

Inactivated microbe vaccine

An inactivated microbe vaccine is one where the microbe is killed—by heat, for example. The inactivated microbe vaccine still contains all the proteins that cause the immunogenic reaction in the host but do not replicate. Thus, the humoral or cell mediated immune response still occurs in response to the immunogens, but the microbe does not replicate. Because they do not replicate in the host, more than one dose may be needed; there may be insufficient numbers of immunogens in one dose to cause the host to mount a full immune response.

Recombinant Protein Subunit Vaccines

The recombinant protein subunit vaccine takes a part of the microbe—the protein found to cause the most immunogenic response in a host—and uses that protein to cause an immune response. Unlike an inactivated virus vaccine, a subunit contains only a small part of the microbe and, therefore, can contain greater quantities of the immunogenic protein. However, like an inactivated microbe vaccine, the immunogenic protein found in a subunit vaccine will not replicate in the body. Subunit vaccines, therefore, normally include an adjuvant, which is a substance that helps amplify, or boost, the host's immune response to the immunogenic protein.

Nucleic Acid Vaccines

Nucleic acid vaccines cause the host's cells themselves to produce microbe-specific immunogens, to which the host's immune system will then respond. Nucleic acid vaccines include both DNA and mRNA vaccines. That is, the vaccine contains either antigen encoding plasmid DNA or RNA either as messenger RNA or viral replicons (virus-like particles that enter a host cell and cause limited transcription and translation but do not produce full viral replications which might cause sequelae associated with that virus).

Autoimmune Disease

When the immune system is unable to differentiate what is self from the host, it will attack the host—causing injury. This process is called autoimmunity. One type of an autoimmune response are allergic reactions. Most autoimmune diseases are the result of both genetic and environmental factors. Some autoimmune diseases result when a self-antigen, which is normally protected from immune cells, becomes exposed to immune cells. For example, some cells within cartilage are normally sequestered from immune cells. However, if injury causes them to be exposed to immune cells, then the immune cells can react to the epitopes on those cells. Autoimmunity also occurs as a result of "molecular mimicry." This occurs when an exogenous antigen has a structural configuration like a self-antigen. In this situation, the immune cells can react both to the exogenous antigen and the self-antigen. This process is thought to be the cause of rheumatic fever following a streptococcal infection. This phenomenon is also seen in connection with viral infections whose molecular epitopes cross react with self antigens.

Autoimmunity can also be induced by certain drugs and hormones, such as estrogen. This is one reason why many forms of autoimmune disease are more common among women. Drugs promote autoimmunity by binding to the surface of cells such as red blood cells which then become a target for the immune system. Fortunately, in such situations, the autoimmune reactivity dissipates once the drug has left the body.

Although not true autoimmune disorders, hypersensitivity reactions ("HSRs") are an example of an injury to the host when the immune system responds excessively. There are four types of HSRs. Types I-III are caused by a humeral response. Type I is driven by an IgE binding to mast cells that can lead to anaphylaxis. A Type IV reaction is referred to as a Delayed-Type Hypersensitivity ("DTH"). An example of a DTH reaction is the dermal reaction to poison ivy. Unlike Types I, II, and III, a Type IV reaction is driven by T-cells. As the name implies, this reaction typically occurs within 48 to 72 hours after antigenic challenge.

Litigation and Immunology

A number of pharmaceutical and medical device litigations over the last 30 years have required defense counsel to develop an understanding of immunology. Some of these litigations allege an immunological basis for the explanation why a plaintiff developed a disease or syndrome. The best example of this was the silicone breast implant litigation. In that litigation, plaintiffs alleged that silicone leaked from the implants and provoked an autoimmune

reaction in women, which caused a number of different diseases and syndromes. Some of the diseases, such as scleroderma and lupus, are well established autoimmune diseases. The etiology of other syndromes, like fibromyalgia, remain unknown decades later. Still other "diseases" were created by plaintiffs' lawyers and their experts specifically for the litigation. These were given different names such as "silicone associated disease."

Another litigation that prominently featured immunology involved latex powdered gloves. The immune reactions experienced by some plaintiffs who were allergic to latex was medically valid. The litigation, however, required defense counsel to understand immune hypersensitivity reactions in order to differentiate true allergic reactions from physical conditions that plaintiffs' experts attempted to associate with exposure to latex allergens.

Litigation has developed over the years involving immune reactions to implanted medical devices, such as orthopedic implants and various surgical mesh products. Litigation has also developed regarding vaccines with allegations such as the now-discredited claim that vaccines cause autism. These examples are only a sampling of the pharmaceutical and medical device litigations that have developed over the last 30 years that have necessitated an understanding of immunology.

Conclusion

As is evident from this overview, the immune system is an incredibly complex and effective system. Were that not the case, we would not survive the daily microbial assaults we encounter. Because of its complexity, the immune system is an attractive target for plaintiffs' experts to grossly oversimplify and, by doing so, mislead jurors. The challenge to defense counsel and their experts is to be able to explain a very complex system in a way that jurors can understand. Hopefully this chapter will help defense counsel meet that challenge.

For readers who want a more detailed explanation of immunology, they are referred to the treatise by Rich, "Clinical Immunology, Principles and Practice" (5th ed. 2018). A shorter and easier-to-read but equally useful text is entitled "Immunology, A Short Course" (7th ed. 2015).

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