Humans interact with an environment teeming with bacteria, fungi, viruses and parasites. Many of these pathogens find their way into the human body through the skin or through the mucus-covered linings of the respiratory and gastrointestinal tracts. As a defense, specialized cells of the human immune system confront, capture and destroy pathogenic invaders. To better communicate and coordinate a response to infection, the various cells of the immune system may travel back and forth between the site of infection and the regional lymph nodes or spleen. These lymphoid organs are key rendezvous points where immune cells exchange information about the invading enemy through biochemical signals, and where they give directions to one another about how to respond to the threat.
The Immune System

The Body’s Armed Services

Military metaphors used to describe the immune system are often apt. The immune system does indeed comprise the body’s armed services. Different branches fulfill different roles in defending the body against bacteria, viruses, fungi and parasites. Immune system success in the battle against these pathogens, like that of any fighting force, depends on getting enough of the right troops in the right place at the right time. As befits these needs, immune cell soldiers are mobile. To reach embattled tissue, they deploy through the bloodstream or via their own system of canals, called lymphatic vessels. The leukocyte cells and organs of the immune system are small and spread throughout the body. But taken together, the components of the immune system are as massive as the brain or liver. During infection, the immune system gets even bigger, and its soldier cells expand their numbers with a speed unrivaled by other cells in the adult organism.

We might fail to appreciate the resources the body dedicates to the immune system if we were not sometimes reminded by swollen tissue, aches, fever, fatigue and inflammation — the byproducts of a vigorous immune response and the evidence of a struggle.

To limit the resources spent on warfare — and our own aches and pains — the cells of the immune system work together, exchanging feedback and mustering just the level of response needed to counter only real threats. Once a threat is eliminated, leukocyte cell populations and immune tissues return to normal size. Failure to mount an adequate immune response to infection can be deadly, but so too can an immune response that is too vigorous, or that fails to wind down once the enemy is vanquished. When the immune system targets harmless particles, the result may be allergy or asthma; when the immune system targets our own tissues, the result is autoimmune disease.

The Battle Plan

As a group, immune cells are often called white blood cells, although immunologists prefer the term leukocytes. A small number of constantly dividing stem cells in the bone marrow, called “hematopoietic” stem cells, generates all blood cells, including leukocytes. (This is why bone marrow transplants, or transplants of the stem cells themselves, can be used to reconstitute immune systems.)

Most immune cells mature in the bone marrow where they first arise. Each type has different duties to perform and, depending upon the nature of the threat, a different battlefield scenario in which to act. It is clear that a functioning immune system depends on the orderly, coordinated deployment of its various components. But, surprisingly, there is no apparent commander in chief. Instead, signals and status reports from cells within the immune system help in the shape and execution of a battle plan. The signals sent between leukocytes, as well as the character of the immune response that unfolds as a result, depend largely on the nature of the pathogen and the site of invasion. Within these parameters, the mobilization and demobilization of immune forces normally unfold according to patterns that immunologists have learned to recognize.

Full-scale immune system mobilization requires the manufacture of more ammunition and weaponry. Most resource-intensive of all, soldier cells of the immune system must enhance their numbers when an invader strikes. This requires massive amounts of protein, which in turn requires that genes within leukocytes be switched on to direct this protein production.

First Line of Defense

The Innate Immune Response

Those immune cells that are ready to fight as soon as bacteria, fungi, viruses or parasites infect us are part of what is called the “innate” immune system. The innate immune system often ends the threat without our ever becoming aware of the danger, thanks to sentinel cells that patrol the outer borders of our body. Phagocytes — cell eaters — are concentrated near the surfaces of nearly all tissues. One of their major tasks is to gobble up invading microbes that get through barriers along these outer borders — the skin or the mucus-covered linings of the respiratory and gastrointestinal tracts, for example.

Phagocytes known as neutrophils, which patrol the bloodstream, are the first to arrive. Other phagocyte troops geared toward rapid response are the macrophages — “big eaters,” which are stationed in all tissues. Macrophages increase their numbers in response to invasion and begin to hit the battlefield en masse shortly after the neutrophils. Natural killer cells, another component of the innate immune system, knock off infected cells that harbor invading viruses.

Even more abundant are dendritic cells. Dendritic cells quickly ferry captured foreign molecules to nearby lymph nodes,
where other immune cells, particularly those known as lymphocytes, garrison themselves. The dendritic cells sound the alert, put the enemy target on display and rouse the garrisoned cells to the challenge.

These brothers-in-arms are called to the fray because leukocytes exchange information and send orders to each other by secreting specialized chemical signals, called cytokines. The process of getting the message from a cell-surface receptor to the cell nucleus, where it can be acted upon, is called signal transduction.

Signal transduction involves specialized proteins inside the cell that integrate incoming signals from cell-surface receptors and transmit gene-switching orders to the nucleus. Failures in signal transduction have been implicated in certain immunodeficiency diseases, in which the immune system is weakened, and also may play a role in some autoimmune disorders.

Different cytokines carry different messages, resulting in a different mix of specially trained immune-cell fighting forces. This makes the forces well-suited to fighting the pathogen of the moment. Among the cytokines, a special class called chemokine guides soldier cells to their fighting destinations via chemotactant signals.

The innate immune response, with its engulf-and-destroy tactics, is a primitive but still vital throwback. Although it quickly responds to pathogens that breach the borders, the weaponry used by its forces is generic — some is anti-viral, some is anti-bacterial, and some works especially well on parasitic worms. It is not tailored to particular enemy species.

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Two Kinds of Immune Response

The immune response has two mechanisms. The innate response involves phagocytes (cell-eaters) and natural killer cells, which patrol the pathogen’s normal points of entry and gobble up invaders or cripple cells harboring viruses. The innate response is generic, immediate and often successful. Should the infectious agent get past this first line of defense, the adaptive immune response — which arises anywhere from three to seven days after the initial infection — sets in motion a different set of fighting forces with weaponry aimed at specific targets. One key feature of the adaptive immune response is that it remembers the enemy (see “All-Out War,” page 17).
T lymphocytes, or T cells for short, are the driving force for the adaptive immune response. The adaptive immune response is a second onslaught launched against invading microbes about three days after the earlier innate immune response, is powerfully and specifically targeted against the particular pathogen that has caused infection. This specificity is made possible by the tremendous variation among T cells. Each T cell is targeted only against a certain molecular marker, called an antigen, found on a particular foreign invader.

**The Adaptive Immune Response**

- **T cell proliferation**
  If the T cell is presented with the pathogen marker it can recognize by one of the immune system’s antigen presenting cells, and if it receives additional “co-stimulatory” signals required for activation, the T cell will expand in numbers. The resultant T cells will mature into fighting forces capable of fulfilling many functions.

- **Macrophage stimulation**
  The immune response is characterized by feedback. For instance, the macrophages that help trigger T cell activation by engulfing pathogens and presenting antigen bits to T cells are in turn spurred to greater activity by mature T cells.

- **Cytotoxic T cells**
  Some mature T cells serve as cytotoxic lymphocytes (CTLs), which target and destroy infected cells.

- **Cytokine production**
  T cells release a variety of signaling molecules, such as cytokines. Some cytokines, such as IL-2, spur specialized T cells to multiply, and some spur inflammatory responses, such as tissue swelling, which serves to limit the spread of infection.

- **Antibody production**
  Mature activated helper T cells can in turn activate their brothers-in-arms, the B lymphocytes, or B cells. B cells make free-floating antibodies that target the same antigen in the blood stream or on the surfaces of infected cells.

Even after the pathogen is defeated, some specialized T cells, called memory T cells, remain. Memory T cells can get the immune response rolling much more quickly and effectively if the same pathogen should ever be encountered again.

**Increasing the Ranks; Aiming at Specific Targets**

While our pre-human ancestors retained an innate immune system during their evolutionary journey, they added additional layers of defense along the way. In the same way that the brain’s primitive cerebellum, sitting atop the brain stem, is in communication with the overlying, highly evolved cerebral cortex, the dendritic cells, phagocytes and natural killers of the innate immune system are in communication with cells from the more evolutionarily advanced branches of the immune system. These more evolved branches, found in almost all vertebrates, are collectively known as the adaptive immune system.

From the time sentinel cells of the innate immune system first detect an infectious threat, full activation of the adaptive immune response takes from three to seven days. An adaptive response involves more fighting forces and weaponry aimed at specific targets.

An extremely important aspect of the adaptive immune system is that it remembers the enemy. When the war is over, a few veteran soldiers of the adaptive immune system stick around. Their presence ensures a faster build-up and a better-honed response if the same microbial foe is ever encountered again.

Vaccines, with bits of weakened or killed pathogen as their centerpiece, are designed to take advantage of immune system memory. The immune system mounts a small response after vaccination, enough to generate veteran lymphocytes (leukocytes that take up residence in the lymph nodes). It is these lymphocytes that will spring into action rapidly if that same enemy reappears in virulent form.

**All-Out War**
Special Forces

**T Cells and B Cells**
The bulk of the troops mustered during an adaptive immune response are called T lymphocytes and B lymphocytes (short-hand for the thymus and the bone marrow, the organs where the cells mature), or simply T cells and B cells. Each lymphocyte is specialized, outfitted to strike target molecules with one particular shape, and to ignore all others.

Suppressor T cells call the troops home when the war is ending.

**B Cells and Antibodies**
Specialized B cells can also target infected cells, as well as secrete mobile versions of antigen-targeting molecules, called antibodies or immunoglobulins. These floating antibodies attack pathogens that roam freely, unassociated with any of the body’s own cells. Antibodies can also neutralize toxins produced by infectious organisms, and like T cell receptors, they can bind to targets on infected cells or on foreign, pathogenic cells, leading to the demise of those cells.

**Antigens and T Cell Activation**
Sentinel cells of the innate immune system must present enemy targets to T cells before the T cells can become activated and in turn activate B cells. The target presented is almost always a bit of protein from a captured pathogen that has been engulfed and repackaged on the surface of the presenting cell. Non-immune, “civilian” cells that are in distress or dying as a result of being invaded by a pathogen also may display targets from the pathogen in slightly different form, like warning flags or distress signals.

A target properly displayed by a sentinel or infected cell fits into a receptor on the surface of the appropriate lymphocyte in lock-and-key fashion. Immunologists refer to these targetable bits of pathogens as antigens. Dendritic cells and macrophages, to a lesser extent, are the main antigen-presenting cells of the immune system. When antigen-presenting cells display captured pathogen targets, and when non-immune cells in distress wave their warning flags, they do so by holding out antigen targets between molecular arms. The arms consist of MHC proteins; “MHC” stands for major histocompatibility complex.

**The Failsafe**

**Co-stimulation**
The engagement of lock and key is a necessary step in the activation of T cells and the initiation of an adaptive immune response. But as a failsafe, another event, called co-stimulation, must also occur. Co-stimulation is governed by proteins that provide “second signals” needed to accelerate T cell activation. Once T cells are activated, the adaptive immune response can really get rolling, with the proliferation of additional T cells and B cells that also specifically target molecular features found on the invading pathogen. When the adaptive immune response comes into play, the innate immune response does not end. In fact, just as the innate immune forces spur the adaptive immune system, so can cytokine signals from T cells, as well as cytokines and antibodies secreted from B cells, in turn rekindle the appetites of microbe-gobbling phagocytes.
Collectively, lymphocytes can create close to a billion different specialized weapons to target just about any molecule, especially protein molecules, that might be encountered on a pathogen. These weapons can also target toxins secreted by pathogens. The immune system can even target molecules the world has never seen before, such as new, man-made chemicals.

For decades, the central mystery of the immune system was how to explain this staggering lymphocyte diversity. It doesn't seem to make sense, given the limited number of genes available to encode so many different receptors. Some esteemed scientists once favored the idea that a single type of receptor can change shape to fit many different targets, like a glove accommodating a variety of hands.

But the real answer to the mystery is that the immune system has an unusual propensity to shuffle and recombine its allotment of the genetic code. The result is millions of sequential permutations, with each reconfigured gene serving as the blueprint for a different receptor or antibody.

Furthermore, enzymes that splice these gene fragments together add bits of DNA at the splice site. In addition, the genes are unusually susceptible to mutation — spelling changes in the DNA sequence. These features combine to further enrich the diversity of lymphocyte receptors made from the genes and to deepen our appreciation for a system that scientists continually seek to demystify and influence in our own best defense.
ADAPTIVE IMMUNE RESPONSE: An immune response that is specifically directed at particular antigens on a disease pathogen. Certain lymphocyte cells of the adaptive immune system retain a memory of prior exposure to antigens from pathogens, including antigens in vaccines. This permits a stronger immune response if the same pathogen is encountered again later.

ANTIBODY: A free-floating, antigen-receptor protein made and secreted by B lymphocytes, specialized for targeting a specific antigen and especially valuable for combating toxins or pathogens that are not inside cells.

ANTIGEN: A molecule that binds to an antibody or antigen receptor.

ANTIGEN RECEPTOR: A specialized protein that populates the surface of a T or B lymphocyte. It permits recognition of pathogen invasion when it binds to its target antigen, in turn leading to the proliferation of lymphocytes and to the inactivation or destruction of pathogens.

AUTOIMMUNITY: A destructive process in which the disease-fighting mechanisms of the immune system are directed against certain of the body’s own molecules, cells and tissues.

BONE MARROW: Spongy tissue concentrated at the core of major bones in which stem cells give rise to all the cells of the immune system, to red blood cells and to the platelet cells that permit blood-clotting.

CHEMOKINE: A large family of cytokines that direct leukocyte movements and govern the migration of leukocytes from the blood to tissues.

CYTOKINE: A type of protein produced by many different cell types that mediates inflammatory and immune reactions. Cytokines are principal mediators of communication between cells of the immune system.

DENDRITIC CELL: A type of immune cell that presents antigens, attached to MHC proteins, to lymphocytes.

EOSINOPHIL: A type of immune cell that is important in defense against parasites.

HYPERSENSITIVITY: A state of exhibiting an uncontrolled or excessive immune response against microbes or harmless foreign antigens, as in an allergic or asthmatic immune response.

INFLAMMATION: A response of the innate immune system in which leukocytes and associated proteins exit the bloodstream to accumulate at sites of infection, toxin exposure or injury. Inflammation is protective but may also sometimes cause tissue damage.

IMMUNODEFICIENCY DISEASE: A disease in which the dysfunction or absence of certain components of the immune system compromises the ability of the immune system to defend against pathogens.

IMMUNOGLOBULIN: An antibody.

IMMUNOTHERAPY: Medical interventions aimed at strengthening an immune response against disease.

INNATE IMMUNE RESPONSE: An early and relatively nonspecific response to infection coordinated by certain cell types, such as neutrophils, macrophages and natural killer cells, and their associated cytokines.

LEUKOCYTE: A cell of the immune system, also called a white blood cell.

LYMPH NODE: A capsule of tissue incorporating many lymphocytes, situated along lymphatic vessels, and a major site for lymphocyte activation by antigen-presenting cells.

LYMPHOCYTE: A cell of the adaptive immune system. Lymphocytes include B and T lymphocytes, which target specific antigens and which are also responsible for immunologic memory.

MACROPHAGE: A type of tissue-based immune cell that engulfs and kills microbes, secretes inflammatory cytokines, and presents antigen to lymphocytes.

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC): A large set of genes that encodes proteins used to display antigens to T lymphocytes.

MAST CELL: A type of immune cell residing near blood vessels, which secretes irritants and plays a major role in hypersensitivity.

NATURAL KILLER: A cell of the innate immune system that kills infected cells and that has the potential to kill tumor cells.

PATHOGEN: An infectious, disease-causing entity. Pathogens include certain bacteria, viruses, fungi, and parasites.

PHAGOCYTE: An immune cell, such as a macrophage, capable of engulfing virus particles or bacteria.

SPLINTER: A lymphoid organ situated in the upper left abdomen that plays a major role in adaptive immune responses to blood-borne antigens.

THYMUS: A lymphoid organ, situated near the lower throat, where T lymphocytes mature early in life.

TOLERANCE: A situation in which the adaptive immune system does not respond to an antigen.

TRANSPLANT REJECTION: An immune response in which a transplanted organ is regarded as a foreign invader, due to a mismatch in donor and recipient major histocompatibility complex proteins, and is attacked by the transplant recipient’s immune system.