



# How the Immune System Recognizes Invaders

*Cells of the immune system recombine gene fragments to create the millions of receptors needed to identify and attack the myriad pathogens encountered throughout life*

by Charles A. Janeway, Jr.

Thirty-six years ago an article entitled "Agammaglobulinemia" appeared in this magazine. One of the authors was my father. In the piece, he described an illness resulting from a defect in the body's defenses against infection, a failure in the immune system's mechanism for detecting pathogens. His work and that of Ogden Bruton in identifying the first known immunodeficiency disease helped to break a path that has led to a deep and useful understanding of how the immune system recognizes and distinguishes the molecules of the body from those of an invading bacterium, virus or parasite.

People who have agammaglobulinemia cannot make antibody molecules. These specialized proteins, found in the blood and extracellular fluid, normally bind to the bacteria or viruses that cause infections and serve as a signal to the attacking molecules and cells of the immune system. The ability of molecules such as antibodies to identify foreign molecules and so to guide the body's defenses confers important advantages. It enables us to eliminate infections, to resist reinfection and to be protected by vaccination.

Some of these same mechanisms, unfortunately, can trigger disease instead of controlling it. The immune system might, for example, react to a harmless foreign substance, such as pollen, producing allergy. Events can take a more serious turn when an immune attack focuses on the body's own tissues, leading to an autoimmune disease. But whether they contribute to health or to dis-

ease, the mechanisms of recognition and response are the same. Recognition mechanisms are therefore crucial to understanding how the immune system works and how it fails.

In this article, I shall describe the two main systems by which the body identifies foreign material. The first is the innate immune system—innate in the sense that the body is born with the ability to recognize certain microbes immediately and to destroy them. The second is the adaptive immune system, in which antibodies play a leading role. The receptors used in the adaptive immune response are formed by piecing together gene segments, like a patchwork quilt. Each cell uses the available pieces differently to make a unique receptor, enabling the cells collectively to recognize the infectious organisms confronted during a lifetime. Understanding the genes, molecules and cells that make up the immune system has enabled researchers to determine the etiology of diseases, including agammaglobulinemia, and to start work on cures.

Our innate immune system can destroy many pathogens on first encounter. An important component of the innate response is a class of blood proteins known as complement. Their name comes from their ability to assist, or complement the activity of, antibodies in fighting infection. Discovered by the Belgian bacteriologist Jules Bordet in 1900, complement can act in many ways. One type of complement protein, when chemically stimulated, can bind to any protein—those on bacteria as well as those on our own cells. The bound protein triggers the activity of the other complement molecules. These bound molecules attract phagocytes, amoeba-like cells that engulf and digest microbes wearing a complement coat. Comple-

ment can also kill cells and bacteria by punching pores in their lipid membrane. The holes allow water to rush in, a process that destroys the cell. Complement protects against such diseases as bacterial meningitis and gonorrhea.

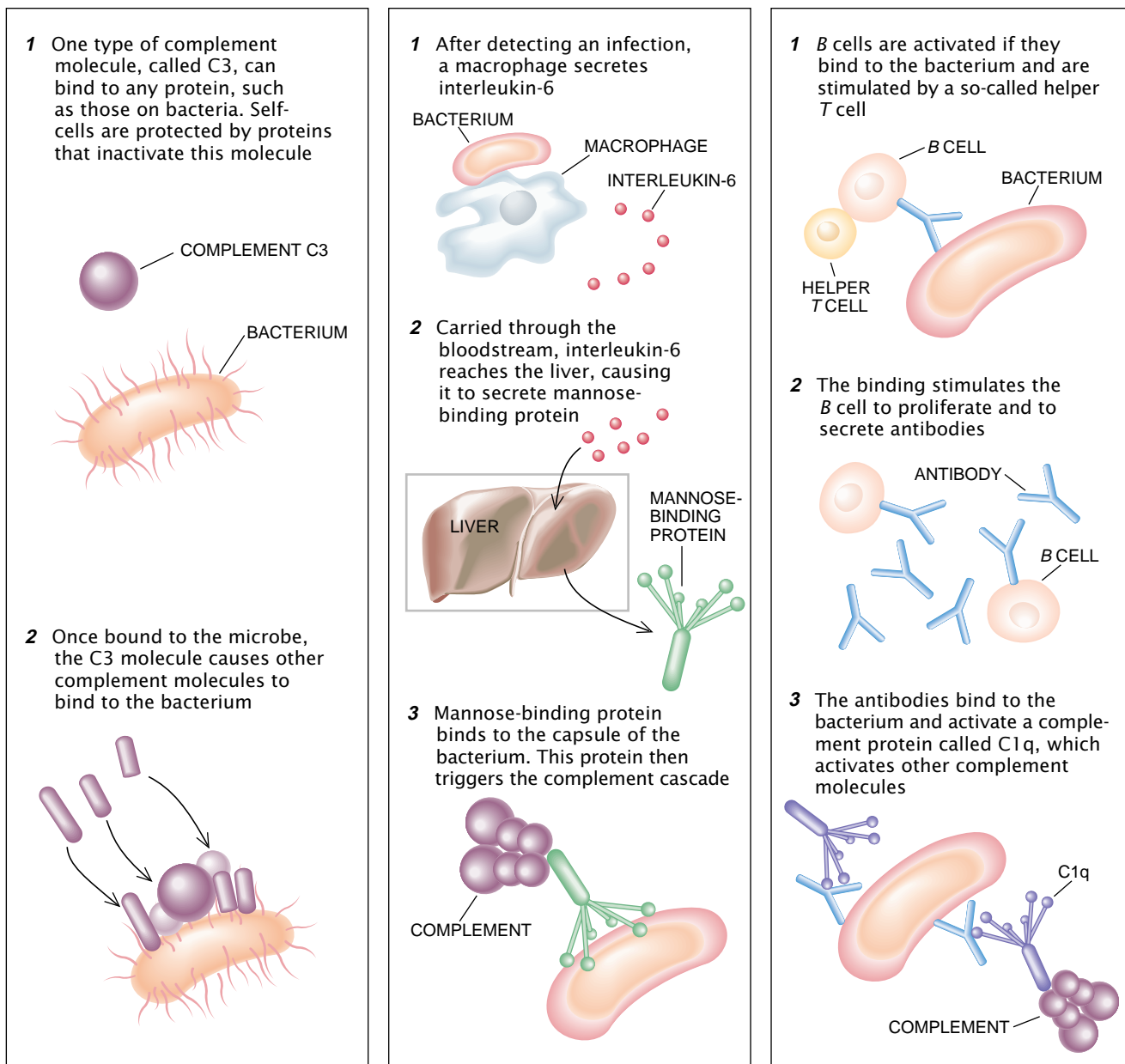
Yet this powerful attack system does not destroy our own cells. Unlike microbes, our cells are equipped with proteins that inactivate complement. Thus, at this simplest of levels, innate immunity distinguishes the molecules that make up the body, called self, from all other molecules, or nonself.

Not all pathogens are so easily disposed of by the complement system. Some have devised ways of avoiding attack by complement. The bacteria that cause pneumonia and strep throat have capsules, coats made up of long chains of sugar molecules (polysaccharides). These capsules prevent complement from acting directly on the bacteria.

The innate immune system has two ways of coping with these types of bacteria. First, throughout the tissues of the body are the large phagocytes called macrophages. Macrophages have receptors for some of these polysaccharides, and they use these receptors to bind to

**T CELLS (yellow), a kind of lymphocyte, use special receptors on their surface to detect an infected macrophage (blue). These T cells represent only part of the repertoire the immune system has to recognize pathogens.**

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**COMPLEMENT ACTIVITY** can be triggered in three ways. Complement can act directly on bacteria (*left*), or it can be activated by mannose-binding protein (*center*). Antibodies produced as a result of infection can also activate complement (*right*). Complement then kills the bacteria or recruits other immune system cells, such as phagocytes.

and ingest bacteria. Second, macrophages that meet bacteria can secrete interleukin-6, a protein that in turn stimulates the liver. Interleukin-6 instructs the liver to secrete a new protein, one that binds to sugar residues called mannose. These residues protrude from the bacterial capsule. After this mannose-binding protein binds to the bacteria, it changes its shape so that it activates the complement cascade and turns on phagocytes. In this way, mannose-binding protein tells the body which particles must be bound.

Innate immunity, however, cannot protect against all infections. Microbes evolve rapidly, enabling them to devise

means to evade the inherited immune defenses of humans and other species that evolve more slowly. To compensate, vertebrates have a unique strategy of immune recognition: adaptive immunity. Adaptive immunity enables the body to recognize and to respond to any microbe, even if it has never faced the invader before.

Adaptive immunity operates by the process of clonal selection, an idea formulated in the 1950s by Sir Frank Macfarlane Burnet of the Walter and Eliza Hall Institute of Medical Research in Australia and now widely accepted. In clonal selection, cells of the adaptive immune system, known as B lympho-

cytes, or B cells for short, manufacture antibodies and display them on the cell surface. The antibody then serves as a receptor. Each B cell makes a different receptor, so that each recognizes a different foreign molecule. Armed with these receptors, the B cells act as sentries, always on the lookout for microbes. If a B cell finds such an intruder, it divides rapidly. Because all the daughter cells come from one parent, they are known as a clone (hence the term "clonal selection"). All the cells in each clone have the same receptor. These cloned B cells then differentiate into cells that secrete antibodies, which, like the B cell receptor, bind to the mi-



crobes. Once flagged as foreign by the antibodies, the microbes are removed from the body by phagocytes and by the complement system.

A critical question in understanding adaptive immunity is how *B* lymphocytes generate so many different receptors. More specifically, how could the millions of different receptors necessary to recognize all microbes be encoded in a limited genome? A person has only about 100,000 genes, but the 10 trillion *B* cells in an individual can make more than 100 million distinct antibody proteins at any one time. We obviously cannot inherit the genes necessary to specify all these proteins.

The answer was discovered in recent years, as investigators identified the genes that encode antibodies and *B* cell receptors. One key was discovered in 1976 by Susumu Tonegawa, then working at the Basel Institute for Immunology. He showed that antibody genes are inherited as gene fragments. These fragments are joined together to form a complete gene only in individual lymphocytes as they develop.

The joining process itself generates still more diversity. In 1980 Fred Alt and David Baltimore of the Massachusetts Institute of Technology showed that the enzymes that combine gene segments add random DNA bases to the ends of the pieces being joined. As a result, new genes, each encoding a protein chain, are formed. Further diversity results from the assembly of protein chains into a complete receptor. Antibodies are made from two pairs of protein chains: a heavy chain and a light chain. The heavy chains are connected to form a Y, with the light chains located on the upper branches, alongside the heavy chains. Each *B* cell produces just one kind of light chain and one kind of heavy chain, so that each *B* cell makes a unique antibody receptor. In fact, 1,000 different chains of each type can in theory form a million combinations. All these random joining processes can create more distinct antibody molecules than there are *B* cells in the body.

As if these processes did not generate sufficient diversity, the genes for receptors of *B* lymphocytes mutate extremely rapidly when the *B* cell is activated by binding to a foreign substance or antigen. These "hypermutations" create additional receptors. In effect, the immune system is constantly experimenting with slight variations on successful receptors in pursuit of an optimal immune response.

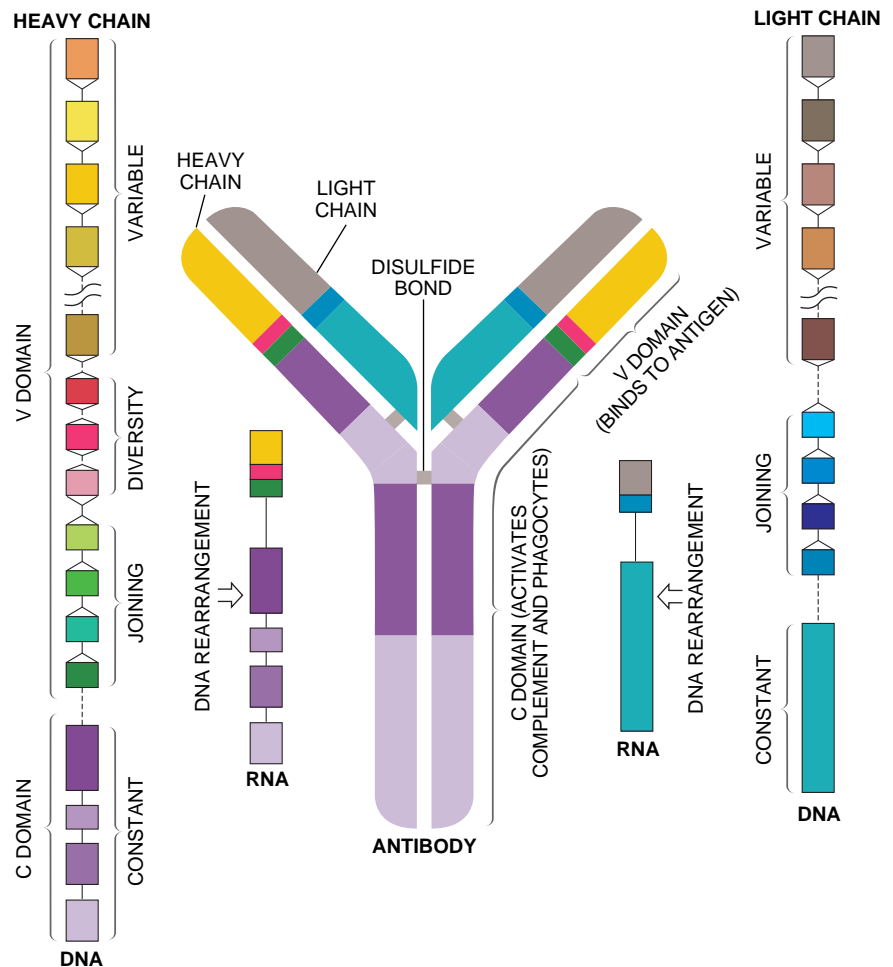
Once a *B* lymphocyte binds antigen to its receptor, it differentiates and secretes antibody molecules—a soluble form of the receptor—into the plasma,

or fluid component, of the blood. Because this new antibody is specified by the genes that created the receptor on the original *B* cell, it has the identical specificity. But a *B* cell and its progeny can produce a different kind of variation on the antibody molecule. It can do this by altering the so-called constant part of the heavy chain, again by rearranging genes. This second type of gene manipulation creates antibodies that go to different places in the body. These antibodies still recognize the same antigens. After binding to a microbe, these antibody types can begin the complement cascade, activate phagocytes or cause allergic reactions.

Adaptive immunity also is the source of immunologic memory. That is, we resist infections we have already experienced far more efficiently and forcefully than we do infections faced for the first time. We have this memory because the body retains lymphocytes that responded in the initial infection.

These cells can be rapidly reactivated when the same types of microbes enter the body, and their antibody products prevent a recurrence of the disease. (In contrast, the innate system does not discriminate one microbe from another and so affords neither more nor less protection after an infection.)

The benefits of adaptive immunity are partially offset by two drawbacks. First, it takes more than five days to develop an antibody response, given that the *B* cells need to proliferate and differentiate before they can make antibodies. The body must rely on the innate immune system to hold infections in check during this period. Second, because any large molecule, such as a protein or a polysaccharide, can be recognized by an antibody, the adaptive immune system on occasion makes antibodies against the body's own cells. These antibodies activate complement so efficiently that the system that prevents complement from attacking the



**ANTIBODY MOLECULE** is made up of a pair of heavy chains and a pair of light chains. The chains are encoded by genes that consist of different DNA segments. These segments rearrange to make genes for chains that are different in each *B* cell. The joining is variable, so that only a few gene segments generate the estimated 100 million distinct antibodies the body is capable of producing.

body's cells is overwhelmed. Autoimmune disease is the result. The attack on self is normally avoided through tolerance, a process that eliminates self-reactive cells [see "How the Immune System Recognizes the Body," by Philippa Marrack and John W. Kappeler, page 80].

**D**espite these drawbacks, the strategy of rearranging genes in adaptive immunity has put in place an ingenious protection system. How could such an elaborate process emerge in vertebrates, and how did it become the keystone in adaptive immunity? As with all evolutionary issues, this question can be answered only in terms of models and not with certainty. Nevertheless, our knowledge of receptors does suggest a plausible scenario.

An important clue lies in the fact that all immunologic receptors are built from similar blocks of protein. Each block is encoded in a chunk of DNA known as an exon, or coding sequence. Exons are divided by introns, noncoding DNA that is transcribed into RNA and then later removed by the process of RNA splicing. As a result, the coding blocks form a continuous message.

Each protein component of an antibody has a structure called the immunoglobulin fold. This general structure is used in many proteins besides antibodies; it forms a compact domain of protein comprising strands of amino acids that lie side by side. In antibodies, these domains form the heavy and light chains, connected by a couple of sulfur atoms, a disulfide bond.

Immunoglobulin domains are of two types, called V for variable and C for constant. The V domains in antibodies pair to make the site that recognizes antigens. They are followed by pairs of C domains that mediate function in the molecule, such as complement binding. The V domains consist of partial genes: a V gene segment, a J (for joining) segment and sometimes also a D (for diversity) gene segment. The unique variability of V domains results from gene rearrangement, which generates the diversity of receptors in humans.

Some proteins, however, have domains that resemble the V domains of antibodies but are not produced by gene rearrangement. In these proteins, a single exon specifies the entire V domain. An example of one such protein is the CD4 molecule, which plays a role in immune recognition and is also the target of the AIDS virus. Such intact V genes are in fact found in some primitive vertebrate antibody genes as well.

Our rearranging antibody V genes likely evolved from these intact V genes. Gene rearrangement could have aris-

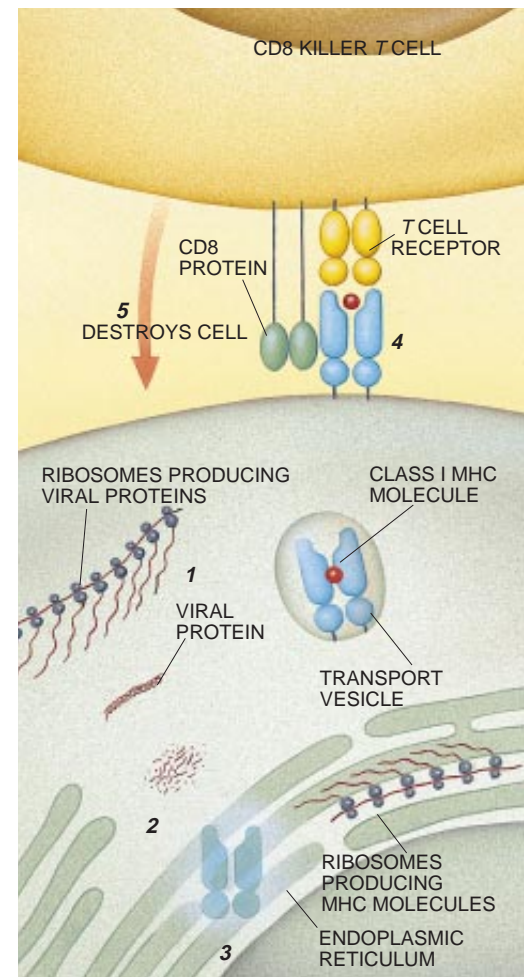
en when a mobile bit of DNA, called a transposon, was inserted into an intact V exon. This insertion split the V exon. Split genes are inactive; they could manufacture antibodies only once the intervening transposon is removed and the gene segments are joined to re-form the intact exon. Just such a removal mechanism exists in our bodies when B lymphocytes generate their receptors. Thus, V gene rearrangement does more than generate diversity in antibodies. It is also crucial in forming the genes that encode antibody proteins. Without rearrangement, no protein can be made from these genes.

Gene rearrangement has proved to be such a powerful means of expressing just one of many related genes that at least one pathogen uses it to avoid detection by the immune system. The trypanosome, a protozoan parasite that causes sleeping sickness, has a single protein in its coat against which the infected host makes antibodies. These antibodies eliminate most of the trypanosomes, but a few of the parasites change their coats by rearranging the coat protein gene. These variant trypanosomes escape detection by the first onslaught of antibodies and continue to grow. The host makes antibody to each variant, but new forms keep arising and growing, causing a relapsing pattern of infection. Here, as in the case of immunologic receptors, rearrangement controls gene expression.

**S**o far we have discussed how the innate immune system, which relies on inherited recognition molecules, and the adaptive system, which relies on gene rearrangement to generate novel receptors in lymphocytes, work together to identify microbes. This dual approach is successful only against pathogens in the body's fluids. Many microbes slip inside the body's cells before antibodies can be made. As water-soluble proteins, antibodies can permeate the extracellular fluid and blood, but they cannot venture across the lipid membranes of cells.

Consequently, the immune system has evolved a special mechanism to detect infections within cells. This mechanism acts in two steps. First, it finds a way to signal to the body that certain cells have been infected. Next, it mobilizes cells specifically designed to recognize these infected cells and to eliminate the infection.

The initial step, signaling that a cell is infected, is accomplished by special molecules that deliver pieces of the microbe to the surface of the infected cell. These molecules, which are synthesized in the endoplasmic reticulum of cells,

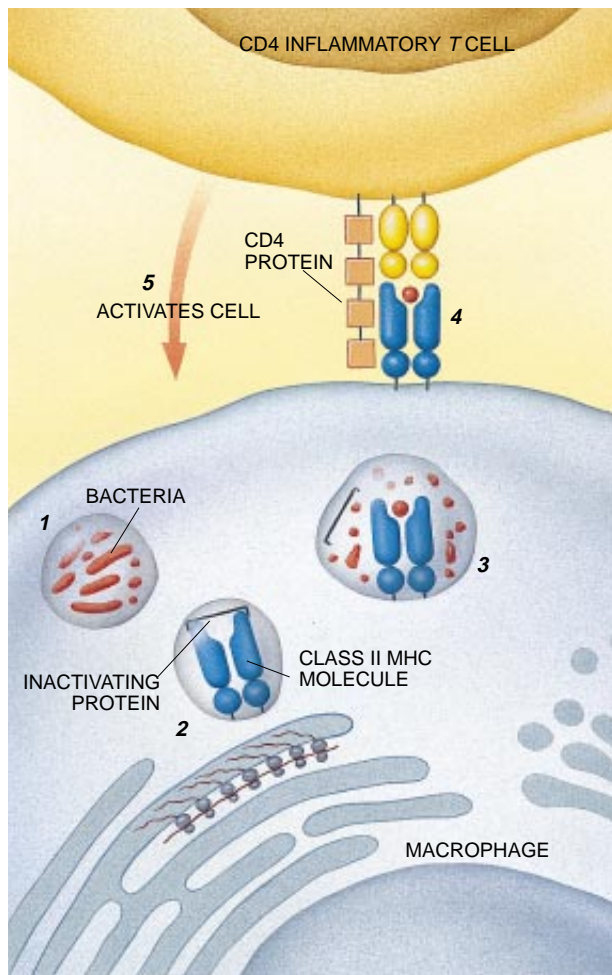


**V**iral proteins produced by an infected cell (1) are broken down into peptides (2). The peptides are taken to the endoplasmic reticulum, where class I MHC molecules form around them (3). Each complex goes to the cell surface. There it can be detected by a killer T cell, which expresses a CD8 protein (4). The T cell then secretes compounds that destroy the infected cell (5).

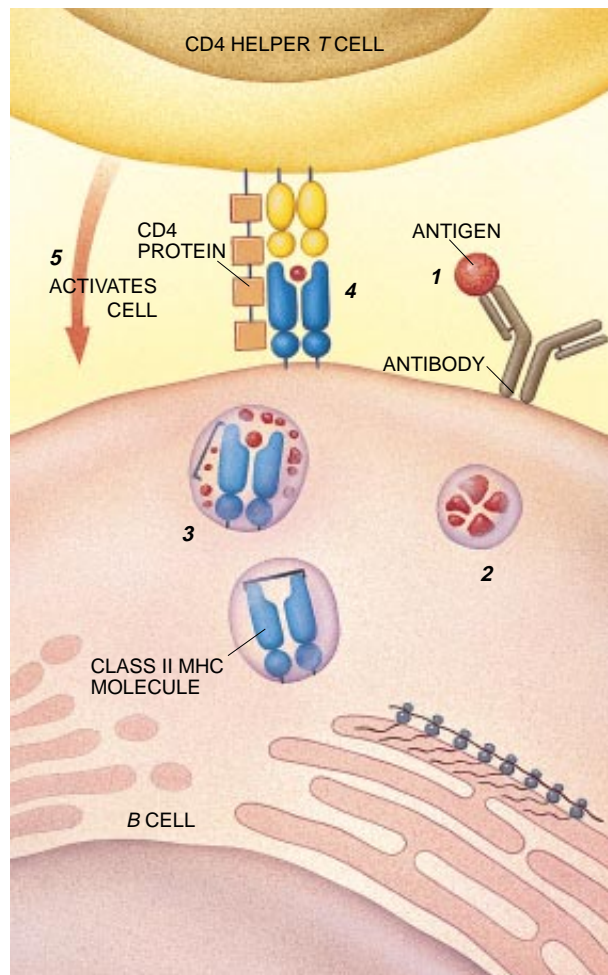
bind to peptides, small fragments of protein that have been degraded inside the cell. After binding to peptides, these transporter molecules migrate to the cell surface.

These transporters are proteins of the major histocompatibility complex (MHC) of genes. They were discovered by the late British geneticist Peter Gorer and by George D. Snell of Jackson Laboratory in Bar Harbor, Me., as the cause of graft rejection; hence their long-winded name, derived from the Greek word for tissues (histo) and the ability to get along (compatibility). These

## Delivering Peptides to the Cell Surface



The bacteria that infected a macrophage reside in the cell's vesicle (1). A class II MHC molecule, produced in the endoplasmic reticulum, is transported to the vesicle (2). A protein chain (black line) keeps the molecule inactive until it reaches the vesicle. In the vesicle the chain falls away, enabling the class II MHC molecule to bind to any peptides there (3). The complex then moves to the cell surface, where a so-called inflammatory CD4 T cell binds to the peptide (4). The T cell then activates the macrophage, signaling it to destroy the material in its vesicle (5).



An antibody on the surface of a B cell serves as the B cell's receptor. If the antibody discovers a foreign antigen in the bloodstream, it binds to it (1) and delivers the antigen to a vesicle inside the cell. The antigen is broken down into peptides (2). A class II MHC molecule, which is produced in the endoplasmic reticulum, migrates to the vesicle, where it grabs a peptide (3). The MHC molecule transports the peptide to the cell surface (4). A CD4 helper T cell binds to the antigen and makes molecules that tell the B cell to proliferate and to produce antibodies (5).

MHC molecules can be divided into two classes, unimaginatively designated class I and class II MHC molecules. Class I molecules are found on almost all types of body cells. Class II molecules appear only on cells involved in an immune response, such as macrophages and B cells.

Although both types of MHC molecules are structurally distinct, studies published this past July by Jerry H. Brown and Don C. Wiley of Harvard University and their colleagues, as well as earlier work by Pamela J. Bjorkman, now at the California Institute of Technology, and her colleagues, showed that

they fold into very similar shapes [see *illustration on next page*]. Each MHC molecule has a deep groove into which a short peptide, or protein fragment, can bind. Because this peptide is not part of the MHC molecule itself, it can vary from one MHC molecule to the next. On healthy cells, all these peptides come from self-proteins. It is the presence of foreign peptides in the MHC groove that tells the immune system that the cell is infected.

The foreign peptide-MHC complexes displayed by an infected cell are recognized by receptors on a distinct type of

lymphocyte, the T cell. The structure of the receptor on T cells is basically the same as that of the membrane-bound antibody molecule that acts as the receptor on B cells. But T cell receptors are specialized to recognize only foreign peptide fragments bound by MHC molecules. When a T cell receptor binds to its specific foreign peptide-MHC complex, the T cell can act to cure or to kill the infected cell.

The two different classes of MHC molecules present peptides that arise in different places within cells. Class I molecules bind to peptides that originate



from proteins in the cytosolic compartment of a cell. These proteins are digested inside the cell as part of the natural process by which a cell continually renews its protein contents. James Shepherd, working in my laboratory at Yale University, recently showed that the short peptide fragments that result from this process are pumped by a distinct transporter from the cytosol into the endoplasmic reticulum.

Here the class I MHC molecules are synthesized as long chains of amino acids that must fold to yield the mature class I MHC protein. This folding can occur only around a suitable peptide, much as a pearl in an oyster develops around a grain of sand [see illustration on page 76]. The peptides transported there, then, make natural seeds.

The folding of a class I MHC molecule around a peptide signals it to carry the peptide to the surface and hold it there. If the peptide is foreign—stemming from, say, a virus infecting the cell—then a passing *T* cell will recognize it. The *T* cells that act in this way are those with CD8 proteins on their surface. These CD8 *T* cells will mount an immune response against the cell by releasing chemicals that destroy the entire cell. Because CD8 *T* cells are programmed to kill cells that display foreign peptides, they are sometimes referred to as killer *T* cells. This response is the only effective way to prevent the creation of more viruses by the infected cells.

Of course, not all microbes grow in the cytosolic compartment of cells. Some bacteria, such as the *Mycobacteria* that cause tuberculosis, grow in vesicles inside a cell, which are sealed off from the rest of the cell by a membrane. Cells infected in this way tend to be macrophages, which engulf bacteria and naturally form a home for such infections. Bacteria in cell vesicles make

proteins that are broken down into peptides within the vesicles. These peptides bind to class II MHC molecules, which then migrate to the vesicles from their origin in the endoplasmic reticulum.

Unlike class I MHC molecules, which must mature around a peptide, class II molecules remain primed for action once they are synthesized. Peter Cresswell, now at Yale, showed that a special chain of amino acids in the endoplasmic reticulum holds the binding ability of class II MHC molecules in check until the molecules move to the vesicles. This extra chain then falls away, enabling the class II MHC molecules to grab hold of any peptides they find.

The class II MHC molecule then delivers the peptide to the surface of the cell. There the peptide can be recognized by *T* cells that have the CD4 protein on their surface. Unlike CD8 *T* cells, CD4 *T* cells do not directly kill the cell. Rather they activate the cells that have displayed the peptide. For instance, one kind of CD4 *T* cell, called inflammatory *T* cells (or Th1), can stimulate a macrophage to kill the *Mycobacteria* inside its own vesicles. It is the loss of this class of CD4 *T* cells that makes patients who have AIDS so susceptible to diseases such as tuberculosis.

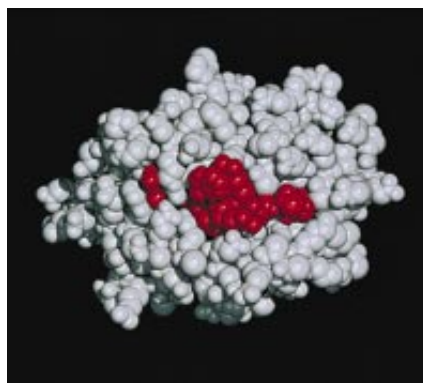
Another kind of CD4 *T* cell—helper *T* cells (or Th2)—guides the activity of *B* cells. When a protein binds to the *B* cell's receptor, the protein is taken to a vesicle, where it is cleaved into peptides that bind to class II MHC molecules. These complexes are then delivered to the cell surface, so that they can be recognized by the helper *T* cells. The helper *T* cells tell the *B* cell to start making antibody, turning on only those *B* cells that have bound to antigen. Thus, even antibody production is ultimately controlled by MHC molecules and *T* cells.

The genes that encode MHC molecules are the most variable ones in humans. This unusual feature of the MHC molecule system may have allowed *Homo sapiens* to survive so many pathogens. Unlike antigen receptor genes, which vary from cell to cell in one person, MHC genes are the same in all of an individual's cells but differ from person to person. Each variant of an MHC molecule will bind different peptides, because the genetic alterations affect mainly the structure of the groove that holds the peptide.

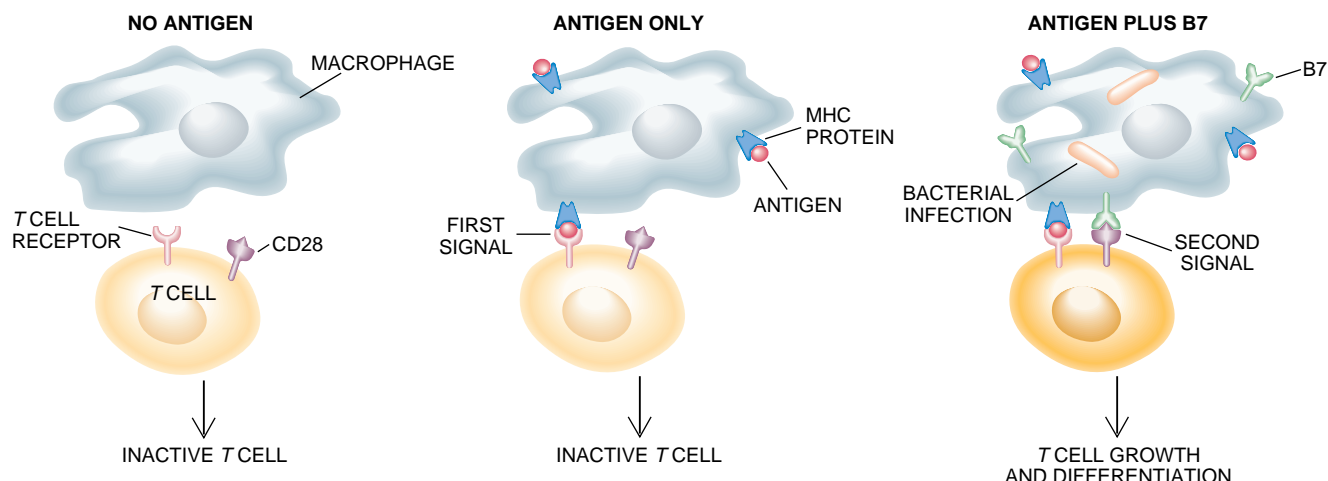
The genetic variability of MHC molecules means that at least some individuals will have MHC molecules that bind to the peptides of any pathogen, even as the structure of microbial proteins evolves. Indeed, A. V. Hill of the University of Oxford has recently studied a population exposed over many hundreds of years to *Plasmodium falciparum*, the parasite that causes fatal malaria. He found that the percentage of people whose MHC molecules bind particularly strongly to peptides from the parasite increased over that time. *T* cells can also recognize these genetic difference in MHC molecules, which explains why tissue grafts are rejected: *T* cells in the host regard the peptides bound by a different MHC molecule as foreign and so kill the grafted tissue.

The binding of antigen to receptor is actually only the beginning of the immune response. For a *B* cell to produce antibodies, or a *T* cell to release its killer or helper molecules, the nucleus of the cell must know that binding has occurred at the cell surface. Lymphocyte receptors are made of several proteins that interact to deliver a biochemical message to the cell's interior. When a receptor binds to an antigen, it causes other proteins in the cell membrane to turn on enzymes inside the cell referred to as kinases. Active kinases add compounds called phosphate groups to other proteins inside the cell. The added phosphate groups change the activity of these proteins so that they ultimately signal the cell to grow and differentiate. The CD4 and CD8 proteins on *T* cells, as well as a protein on *B* cells known as CD19, are examples of membrane proteins coupled to kinases inside cells. Another kind of molecule that goes into action is CD45, an enzyme that helps to mediate lymphocyte activation by removing phosphates from certain proteins, thereby deactivating them.

But kinase-mediated signals cannot by themselves activate lymphocytes. Lymphocytes must receive a second signal derived from other cells in the body



**MAJOR HISTOCOMPATIBILITY COMPLEX, or MHC for short, makes two kinds of molecules in cells: class I (left) and class II (right). The images present the viewpoint of a *T* cell receptor. Class I MHC molecules can hold only short peptides (red), because the binding site is closed off. In contrast, class II MHC molecules can bind to peptides of different lengths, because the binding site is open at both ends.**



**STIMULATION** by two molecules is needed to activate lymphocytes. The diagrams depict a CD8 *T* cell and a macrophage. Without the presence of antigens, the *T* cell is dormant (left). Yet antigen alone cannot induce *T* cell function (center). In this way, a response to the body's own antigen does not occur; in fact, this first signal turns off the *T* cell. If the macrophage is infected, it will produce a molecule called B7, which acts on the *T* cell's CD28 surface protein (right). Only when an antigen and the B7 molecule are present on the same cell does the *T* cell proliferate.

to grow. These messages are often called costimulatory signals. *B* cells require helper *T* cells not only to recognize antigen but also to make a protein—CD40 ligand—that binds to the *B* cell molecule CD40. *T* cells rely mainly on so-called B7 molecules as costimulatory signals; such molecules are expressed by the same cells that present antigen. While working in my laboratory, Yang Liu, now at New York University Medical Center, showed that B7 is expressed when the innate immune system recognizes that microbes are present, that is, usually during the early phases of infection. In effect, the innate system may prime the adaptive system for action. In this way, costimulatory signals may also assist the adaptive immune response in differentiating infectious microbes from self-tissues. Lymphocytes that bind to antigen but do not receive costimulation are not activated. As a result, self-antigens alone would not be able to initiate an immune response.

Once a lymphocyte binds to antigen and receives costimulation, it differentiates and becomes active. (The active versions of lymphocytes are sometimes called effector cells, as they actually mediate the immune response.) Once activated, the cell no longer requires the costimulatory signal. Thus, although only cells that express costimulators can elicit an immune response, any cell or molecule can be targeted. This response is important because it enables *B* and *T* cells to attack any cell that has become infected, regardless of its type.

So what is wrong in patients who have agammaglobulinemia, a condition

in which antibodies are not made? The answer has only recently been discovered [see "How the Immune System Develops," by Irving L. Weissman and Max D. Cooper, page 64]. It turns out that during the development of *B* cells in healthy individuals, the rearrangement of receptor genes is carefully regulated. In other words, the antibody receptor must be manufactured accurately. The V gene for each chain has to be rearranged in the right sequence, and the receptor cannot be completed until all the rearrangements are correctly made.

**T**hus, to form correct receptors, the cell must determine the state of its receptor genes as development proceeds. A heavy-chain V gene is rearranged so that a cell can make the heavy chain of its receptor first. This chain goes to the cell surface. The presence of the heavy chain at the cell surface signals the *B* cell to stop rearranging heavy-chain genes and to start rearranging light-chain genes. A kinase seems to deliver this crucial message from the cell surface to the interior.

In agammaglobulinemia, heavy chains are made, but light chains are not. In these patients, a kinase has recently been found to be defective. (Interestingly, absence of a related kinase found in *T* cells has an identical effect on *T* cell development.) Apparently, the gene defect described by my father in these pages 36 years ago has finally been identified, and we should soon understand how it works.

Meanwhile the kinds of infection that occur in people with agammaglobulinemia have taught us why antibody pro-

duction is necessary for health. Treatment of these patients with immunoglobulins pooled from donors provides them with antibodies and allows a nearly normal life. But this therapy is only a temporary repair for a genetic disease that can now, in theory, be corrected by inserting the normal gene into a patient's bone marrow cells. Continued strong support for basic research in immunology, genetics, cell biology, cancer and molecular biology is needed to conquer this and the other more prevalent diseases discussed in this issue.

#### FURTHER READING

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- PHYLOGENETIC DIVERSIFICATION OF IMMUNOGLOBULIN GENES AND THE ANTIBODY REPERTOIRE. Gary W. Litman et al. in *Molecular Biology and Evolution*, Vol. 10, pages 60-72; January 1993.