

RESISTANCE AND IMMUNITY

Raluca Popovici*

* University of Oradea, Faculty of Environmental Protection, 26 Gen. Magheru St., 410048 Oradea;
Romania

Abstract

While the parasite uses all the means at its disposal to establish infection, the host's body has a number of defense mechanisms to prevent infection. The intricacies of the host-parasite relationship are many and varied, and one cannot be considered without the other. The ability of a host's body to prevent or overcome invasion by pathogenic microorganisms.

Natural resistance provides defense against infection by a number of mechanical and chemical barriers. The skin and mucous membranes, mucous secretions, enzymes, and components of the blood and other body fluids are examples of this type of barrier. Lack of such natural resistance is called susceptibility.

Key words: antigens, immunoglobins, phagocytosis.

The acquired type of resistance, immunity, is a very important factor in warding off infection. It is usually due to the antagonism between pathogens and specific substances known as antibodies, which are formed by the body in response to stimulation by foreign substances called antigens. Antibodies are usually specific for a given organism. Although they may occur "naturally," they are customarily manufactured by the host in response to a stimulus provided by a pathogen, or a part of it, in the body.

NATURAL RESISTANCE

Natural resistance depends on such a large number of factors that only a few of the most important are mentioned here. The general health of the host, the state of its nutrition, social and economic conditions, and other nonspecific factors all play a part, but their roles are so interlocked that it is difficult to evaluate their individual importance.

INDIVIDUAL RESISTANCE

Some people have one cold after another, while others never "catch cold"; yet both apparently have the same chances for exposure. In some families with several children, all but one may have simultaneous cases of chicken pox, measles, or other such diseases. These are examples of individual resistance, which may be due to a single factor or a combination of several. Anatomical abnormalities may increase a person's

apparent susceptibility to an infection, and state of nutrition, personal hygiene, and opportunity for exposure to infectious microorganisms influence his or her capacity for resistance.

EXTERNAL DEFENSE MECHANISMS

The host body has two lines of defense that must be overcome by a pathogen before it can establish an infection. The first line of defense is largely mechanical, but chemical factors are also involved; these may be grouped as external defense mechanisms.

Mechanical barriers include the unbroken skin and mucous membranes, which are generally impervious to infectious agents. It is possible for microorganisms to enter through hair follicles, openings of sweat glands, or abrasions, but skin and mucous membranes form a generally effective barrier.

IMMUNE RESPONSES

Immune responses are processes in which animals form specifically reactive proteins and cells in response to a great variety of foreign organic macromolecules and molecules. These responses are found only in vertebrates and constitute an important means of defense, not only against infection by pathogens but probably also against host cells that become cancerous.

ANTIGENS

The terms antigen and antibody are so closely interdependent that mention of one usually involves the other. Any substance which when introduced into the body gives rise to the production of antibodies is an antigen. It also reacts observably with its antibody. Thus an antigen has two properties: immunogenicity, or the capacity to stimulate the formation of the specific antibodies, and reactivity, or the ability to react specifically with these antibodies.

Antigens may be proteins, nucleoproteins, lipoproteins, many polysaccharides, numerous synthetic polypeptides, and many small molecules (haptens, see below) suitably linked to proteins or to synthetic polypeptides. Usually they are substances foreign to the body in which they act to produce the antibody response. Many substances may act as antigens: bacteria, viruses, and other microorganisms; foreign proteins such as pollens, egg white, and metabolic products of microorganisms; and blood cells from a different animal species. Antigens stimulate the production of

substances that may have prophylactic or therapeutic properties against the specific organism that is the antigen. The antigenicity of a substance is not, however, related to its ability to produce disease or damage tissue. Antigenicity can be measured only in terms of the antibody response it produces. Antigens consist of more than one functional part: a portion responsible for specificity (reactivity) and a portion responsible for the stimulation of antibodies (immunogenicity) in the animal body. Antigens having specificity as well as immunogenicity are called complete antigens. The portion responsible for specificity can be separated from the antibody-inciting portion. The specificity portion reacts with specific antibodies but it cannot incite antibody production. Such fractions are called partial antigens or haptens. The specificity of complete antigens and haptens is due to their ability to bind with related chemical structures on the antibodies.

TYPES OF ANTIGENS

We have seen that many proteins, polysaccharides, and other substances are antigenic. For example, the blood serum or cells of one species of animal may be antigenic when introduced into another species. If an individual is sensitized by one injection containing a small amount of horse serum, a severe reaction may occur when subsequent injections of material containing horse serum are given.

Antigens present in human red blood cells in some persons react with isoantibodies (from the Greek word meaning "same") in other persons. Because there are several different antigens associated with human red blood cells, there are several blood groups, the best known being O, A, B, and AB.

TOXOIDS

Toxoids are made by destroying the poisonous portions of toxins without altering the antigenic portion. Toxoids are used antigenically for protecting individuals against diphtheria, tetanus, and other diseases caused by toxins or toxin-producing microorganisms.

ANTIBODIES

As we have seen, in addition to phagocytes, blood contains circulating antibodies which defend the body from infection. Antibodies have already been defined as specific substances formed by the body in response to stimulation by antigens. Chemically, they are proteins.

IMMUNOGLOBINS

All proteins that function as antibodies are now known by the general term immune/globulin. Every antibody molecule is characterized by two functions: (1) specific binding and (2) participation in a limited number of general or effector reactions, e.g., allergic reactions, complement-fixation. The two functions are carried out by different parts of the antibody molecule. In each animal species, the immunoglobulin molecules can be divided into different classes on the basis of the structure of their "backbone." Human immunoglobins are divided into five principal classes: immunoglobulin G (abbreviated IgG), IgM, IgA, IgD, and IgE. (They may also be referred to as yG, yM, yA, yD, and -yE.) Let us see how these structural classes are named. Every antibody molecule consists of two pairs of polypeptide chains. Because the chains of one pair are longer and have a greater molecular weight than those of the other, the chains are classified as heavy.

The light chains can be either kappa or lambda, depending on their serological reactions with special antisera; in any one immunoglobulin molecule both light chains are always of the same type. There are five types of heavy chains: -y, J μ L, a, 8, and e (Greek letters for gamma, mu, alpha, delta, and epsilon). These determine the immunoglobulin class of the antibody as mentioned above. Some immunoglobulins also have additional polypeptides, and some form oligomeric associations of from two to five units (each unit consisting of paired light and heavy chains). In addition, some of the classes contain multiple subclasses.. The terminal portions of both heavy and light chains (at the antigen-binding-site end) show considerable variation, whereas the remaining parts of the chains are relatively constant in structure. Thus the amino acid sequence of the constant regions determines the class or biological role of an immunoglobulin, and the variable regions determine its specificity.

IgG. Some 85 percent of the immunoglobulins in normal sera is, IgG can be differentiated into four subclasses (IgG-1 through IgG-4), each with a distinctive heavy chain. All these subclasses have been detected in normal human sera: IgG-1, -2, -3, and -4 make up approximately 70, 19, 8, and 3 percent, respectively, of the IgG proteins.

IgM immunoglobulins have one additional polypeptide, J, per 10 light chains. Its function is not known although it may be responsible for stabilizing the multimeric forms of IgM. About 6 percent of the total immunoglobulin is IgM.

IgA. This constitutes about 10 percent of the total immunoglobulin in sera, IgA is also found in exocrine secretions (secretions of milk,

respiratory and intestinal mucin, saliva, and tears). Human sera IgA occurs mostly as the monomer; exocrine IgA is largely a dimer.

IgD. This constitutes only about 1 percent of total immunoglobulin in normal sera. IgD may be an early receptor which later gives way to IgM and other immunoglobulins.

IgE proteins are responsible for severe, acute, and occasionally fatal allergic reactions. These include drug sensitivities, allergic asthma, anaphylaxis, and hay fever.

Antibodies react against specific microorganisms, their toxic products, and other compounds. They can be used in the treatment of infection caused by the homologous microorganisms, and, more importantly, they prevent infection and disease caused by these agents. Antibodies are designated by names that describe their reaction in vitro or in vivo, when they are allowed to act on certain types of antigens: (1) antitoxins, (2) agglutinins, (3) precipitins, (4) lysins, (5) complement-fixing antibodies, (6) opsonins, and (7) neutralizing antibodies.

These antibodies are all produced as a result of antigenic stimulus and are present in blood serum. They are called humoral antibodies and can be differentiated as follows:

- 1 Antitoxins neutralize toxins.
- 2 Agglutinins cause clumping of the bacterial cells for which they are specific.
- 3 Precipitins cause precipitation or flocculation of extracts of bacterial cells or other soluble antigens.
- 4 Lysins cause dissolution of bacterial or other cells that are specifically sensitive to their action.
- 5 Certain antigen-antibody reactions require that complement be present to bind the reactants together. In so doing the complement is "fixed," or used up.
- 6 Opsonins render microorganisms more susceptible to ingestion by phagocytes.

Neutralizing (protective) antibodies protect against infection by neutralizing the infectivity of the pathogen or by neutralization of toxin

PHAGOCYTOSIS

The importance of phagocytosis in protecting the body from infection was first recognized by Metchnikoff in 1882. He believed that cellular activity, in destroying bacteria and other microorganisms, was the primary defense mechanism of the body. Neutrophils (polymorphonuclear leukocytes) and macrophages (reticuloendothelial-system cells) are the principal cells involved in phagocytosis or the ingestion and killing of

bacteria Neutrophils constitute the front line of internal defense for the host. They are produced in large numbers in bone marrow and circulate in the blood for 6 to 7 h. They then penetrate blood-vessel walls by squeezing through endothelial cell junctions. The neutrophil is a short-lived cell which does not divide after leaving the bone marrow and survives in tissues for only a few days. The turnover rate (new ones replacing old ones) of neutrophils is about 10^{11} daily. Neutrophils are equipped with numerous enzymes and antimicrobial substances for the killing and degradation of bacteria. Such substances are contained in membrane-bound organelles called lysosomes.

Macrophages are also formed in the bone marrow from a precursor cell but unlike the neutrophils are long-lived and can persist in tissue for weeks or months. Most macrophages that are found in tissue, in the peritoneal cavity, or within the alveoli of the lung come from blood monocytes which migrate from the blood into these areas. Under certain conditions, macrophages can synthesize new DNA and multiply. Because of their capacity for differentiation, in tissue they are called tissue histiocytes; in the liver, Kupffer cells; and in the lung, alveolar macrophages.

COMPLEMENT SYSTEM

Complement is normally present in serum and consists of a group of related proteins. It is called complement because of its complementary effect on certain immune and allergic reactions involving antibodies. As a resistance factor, it is now recognized that the invading cells are attacked by complement; the function of the antibody is to identify the invading cell and activate the complement attack. When complement is activated by antibody, it is not only detrimental to invading foreign microbes but also to the host's own cells. But this self-destructive activity is minimized by the antibody which fixes complement on the surface of the invading cell.

There are several characteristics to the complement system. It has a recognition unit to respond to the antibody molecules that have identified an invader. It has receptor sites to combine with the surface of the foreign cell when it is activated. Its activity must be limited in time to minimize damage to the host's own cells. This limitation is brought about partly by spontaneous decay of activated complement and partly by interference from destructive enzymes and inhibitors.

The complement system has 11 proteins designated by the letter C and by number: C1, C2, . . . C9. C1 consists of the subunits C1q, C1r, and C1s. Complement proteins may also be fragmented enzymatically, for example,

C3 to C3a and C3b. They carry out a sequence of events in complement recognition, activation, and cell attack.

Cell attack results in cell-membrane damage, leading to cell lysis.

Among the many activities of complement, in addition to cell attack, are immune adherence (mentioned previously), chemotaxis, and release of histamine. These activities are an important part of the inflammatory response.

The C3a and C5a fragments cause the release of histamine from cells (leukocytes, mast cells, and platelets) that store it. Histamine increases the permeability of capillaries enabling leukocytes to penetrate into tissues where an infection or allergic process is underway. C5a and other fragments (C3a and C5bC6C7 complex) are chemotactic for certain leukocytes; i.e., they cause the leukocytes to migrate toward the site from which the chemotactic agents are diffusing. This promotes accumulation of leukocytes at tissue sites where immune reactions are taking place.

The processes which protect the body against invading cells can also produce undesirable effects, collectively termed allergy or hypersensitivity. One particular extreme effect is anaphylaxis, an untoward reaction to foreign antigen, which may occur following repeated exposure to the same antigenic substance. Anaphylaxis, which can be severe enough to cause death, is due to an antigen-antibody reaction that brings about the massive release of histamine. Complement is also involved in anaphylaxis because fragments C3a and C5a were found to induce the release of histamine from some cells. Anaphylaxis in some individuals can be brought about by bee and wasp stings and by injection of certain drugs like penicillin. Less severe anaphylactic reactions include inhalation of allergens, such as ragweed pollen, or ingestion of certain foods; these involve IgE.

INTERFERON

Interferon is a nonspecific antiviral agent which inhibits intracellular viral replication and is synthesized by cells in response to viral infection. Interferons were discovered in 1957 by investigators working on the mechanism of viral interference (resistance of an animal or cell infected with one virus to superinfection with a second unrelated virus). The lack of virus specificity exists because interferons do not react directly with the virion but rather exert their protective effect by an intracellular mechanism. Interferons are specific with regard to the species of cells that produced them, produced by human cells primarily protect human cells and have little protective capacity for mouse cells, chick cells, etc.

Interferon causes antiviral resistance indirectly by inducing the synthesis of an antiviral protein by exposed cells. This means that protection by interferon is afforded by an intracellular induction of host metabolism leading to the subsequent synthesis of another set of molecules, the antiviral proteins. Since the inhibition of virus is not a direct one, it is not surprising that interferons are not virus-specific but cell-specific. Our interest in interferon, in the context of the present chapter, is obviously in its antiviral effect in preventing cell infection. This is but one facet of interferon activity. There are other aspects which should interest the microbiologist, e.g., interferon effect on cell-membrane-related events, immune responses, cell-growth depression and modification.

Unfortunately, interferons are relatively unstable in tissue fluids. For this reason, interferon for antiviral therapy is not particularly useful clinically. But interferons may play a protective role during naturally acquired viral infections because they are produced more promptly than specific antibodies.

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