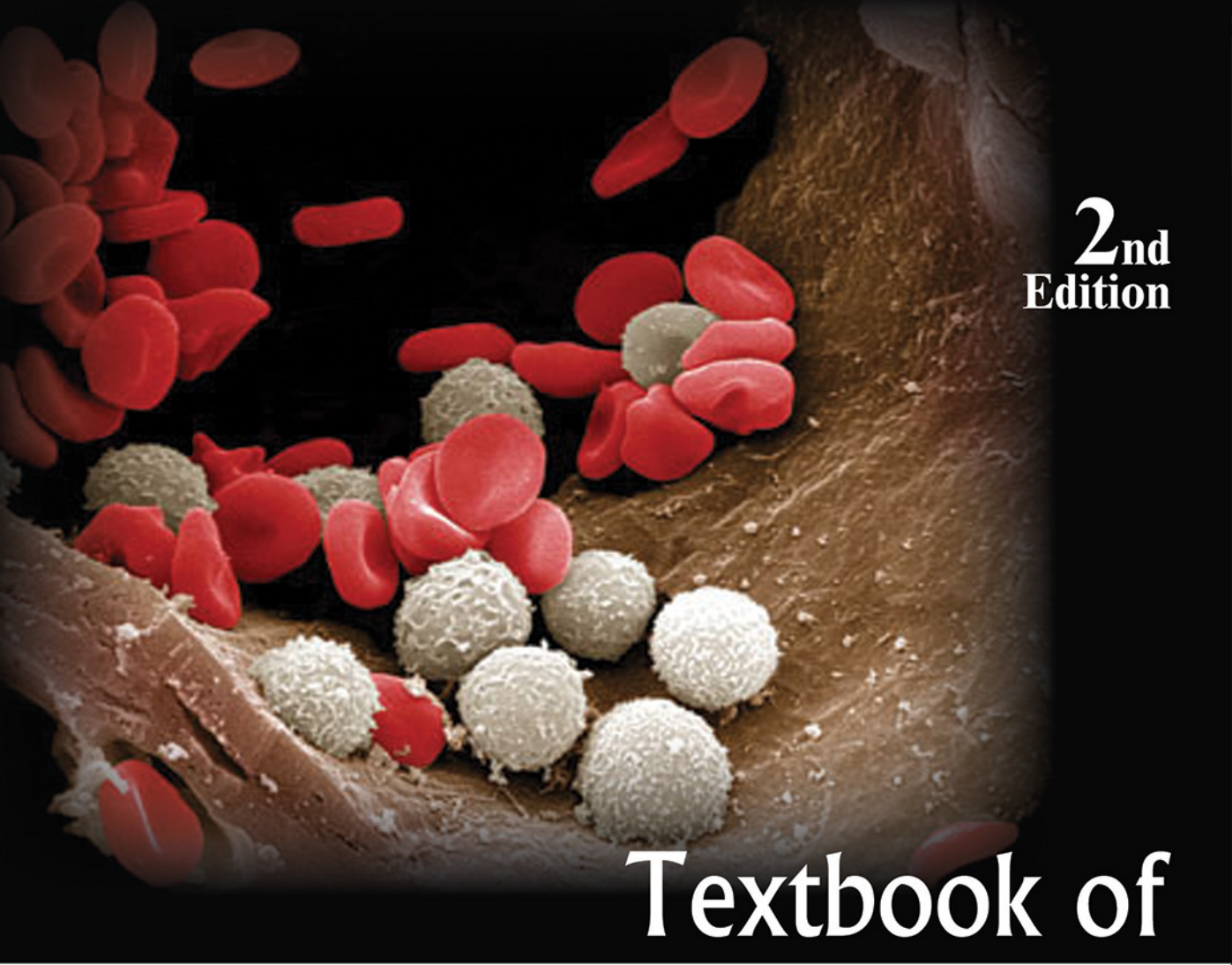


2nd Edition

Textbook of IMMUNOLOGY

Sunil Kumar Mohanty
K Sai Leela

Foreword
KC Nathsarma

JAYPEE

Contents

3 Immunity

Pathogenic microorganisms are endowed with special properties that enable them to cause disease, if given the right opportunity. If microorganisms never encounter resistance from the host, we would constantly be ill and would eventually die of various diseases. But in most cases, our body defenses prevent them of happening so. In some instances, the body does not allow the organisms to enter. In others, even if they enter, are eliminated by different mechanisms. In still others, even if they remain inside, the defenses combat with them. Our ability to ward off disease in general is called resistance (immunity). Vulnerability or lack of resistance is susceptibility.

Immunity is defined as the resistance exhibited by the host towards injury caused by the microorganisms and their products.

Protection against the infectious agents is only one of the consequences of the immune response. But in true sense, immunity involves the defensive response, when a host is invaded by foreign organisms or other foreign substances (pollen, insect venom, transplanted tissue). Body cells that become cancerous are also recognized as foreign and may be eliminated.

TYPES OF IMMUNITY

Immunity to infectious agents can result from innate immunity, acquired immunity or both (Fig. 3.1).

Innate Immunity

Innate immunity is an invariable, hereditary response—an inborn defense. It is independent of previous exposure to disease causing agents and foreign substances. The innate immunity depends on the non-specific mechanisms, molecular defenses and the activity of the phagocytic cells. Innate immunity may be non-specific, when it indicates a degree of resistance to infection in general or specific, when resistance to particular pathogen is concerned.

Innate immunity may be considered at the level of species, race and individual. In species immunity, all individuals of a species are born with resistance to an infectious agent that causes disease in another species. For example, humans are immune to most infectious agents that causes disease in pets and other domesticated animals. Human beings are insusceptible to rinderpest or distemper, which the canines suffer. Similarly, the animals show innate immunity to many human pathogens. The mechanisms of species immunity are not clearly understood, but may be due to physiological and biochemical differences between the tissues of the different host species that determine, whether or not a pathogen can multiply in them.

Within a species, different races show difference in susceptibility to infections. This is known as racial immunity. The classical

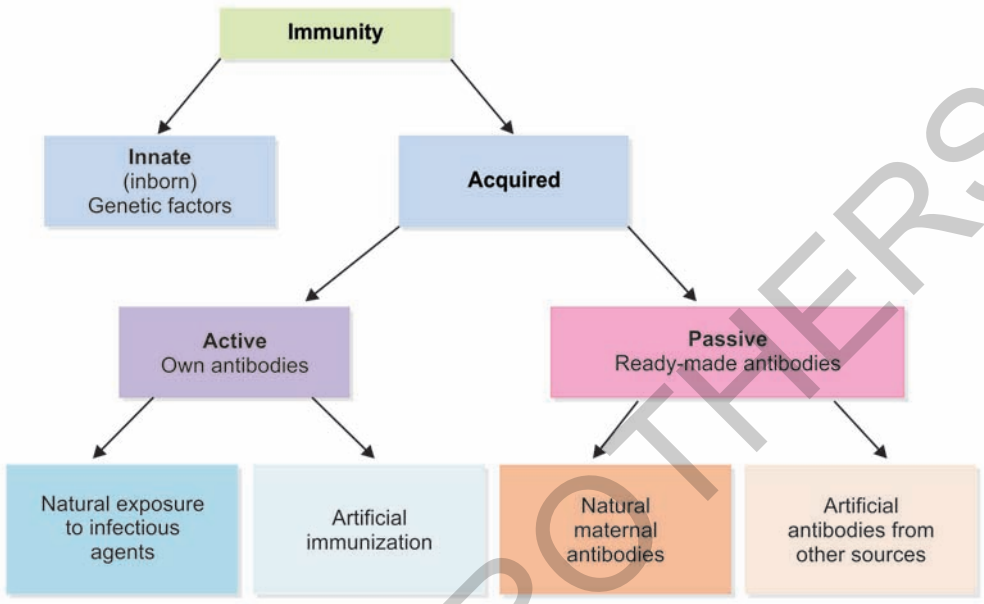


Fig. 3.1: Various types of immunity. Non-specific immunity is largely innate or inborn, whereas specific immunity is acquired.

example of racial immunity is the resistance to anthrax by Algerian sheep, where as sheep in general are susceptible to anthrax. It has been reported that the Negroes in the USA are more susceptible to tuberculosis than the whites. An interesting instance of genetic resistance to *Plasmodium falciparum* malaria is seen in some parts of Africa, where sickle cell anemia is prevalent. The hereditary abnormality of the red cells confers immunity to infection by malaria parasite. Even resistance to human diseases, such as measles, can vary from person to person. For example, although the effect of measles is usually relatively mild in European ancestry, the disease devastated the population of Pacific Islanders, when they were first exposed to measles by European explorers. Natural selection resulting from the exposure of many generations to the measles virus, presumably led to the more frequent inheritance of genes that conferred some resistance to the virus.

Individuals in a race exhibit difference in innate immunity. The genetic basis of individual immunity is evident from studies on the incidence of infectious disease in twins. Homozygous twins exhibit similar degree of resistance or susceptibility to lepromatous leprosy and tuberculosis. An individual's resistance to disease also depends on age, nutritional status, stress, hormone influence and general health in addition to genetic factor.

Age: Two extremes of life carry higher susceptibility to infections in comparison to adults. The heightened susceptibility of the fetus to infection is related to the immaturity of the immune system. In neonates, the antibodies, immune competent cells and also the complement level remain suboptimal. The fetus in uterus is normally protected by the maternal antibody, but some organisms (*Toxoplasma gondii*, rubella virus, cytomegalovirus,

herpesviruses, *Treponema pallidum, Borrelia burgdorferi,* hepatitis B virus, human immunodeficiency virus, etc.) cross the placental barrier and cause respective diseases. Newborn animals (suckling mice) are more susceptible to coxsackievirus.

Tinea capitis caused by *Microsporum audouinii* is very common in young people, which disappear after reaching puberty. The vaginal epithelium of prepubertal girl is more susceptible to gonococcal infection.

Some infections like poliomyelitis and chickenpox, tend to be more severe in adults than in young children due to hypersensitivity that causes more tissue damage. The old people are prone to infection due to waning of the immune system. The immune system shows the senescence seen in other organs. Cellular immunity is most affected.

Hormonal influence: Diabetes, hypothyroidism and adrenal dysfunctions are associated with enhanced susceptibility to infections. Corticosteroids depress host resistance by anti-inflammatory and antiphagocytic effects and also by suppressing antibody formation. The elevated steroid level in pregnancy may have a relation to the heightened level of susceptibility to the staphylococcal infection.

Nutrition: The interaction between malnutrition and immunity is very complex. But in general, malnutrition depresses both cell-mediated immunity (CMI) and antibody-mediated immunity (AMI). CMI and AMI responses to T cell-dependent antigens are primarily reduced in malnutrition.

Paradoxically, there are some evidences that the infections may not be clinically apparent in ill nourished and malnourished patient. Fever in malaria may not be induced in famine-stricken area, but once that nutrition is improved fever appears. Some viruses may not multiply in the tissue of several malnourished individual.

Stress: Whether psychological or physical, stress adversely affects the immune response.

Mechanism of Innate Immunity

First line of defense

Physical barriers: Skin and mucous membrane form an important line of defense. Intact skin is impenetrable to most of the bacteria. Its low pH and presence of fatty acid makes the environment inhospitable for bacteria other than commensals. The continual shedding of the squamous epithelium also reduces bacterial load. If the continuity of the skin is compromised, the skin may be secondarily infected.

The mucous membranes form a less formidable barrier. The mucus with entrapped bacteria is swept away by cilia of the ciliated respiratory mucosa or the villi in the intestine particles are swallowed and coughed out by cough reflex.

The flushing effect of the body secretions reduces the microbial flora. Any slowing of urinary flow increases the chance of ascending infection. Saliva teeming with oral bacteria flows to the back of throat and is swallowed; gastric acidity destroys most swallowed bacteria. Commensal flora in the intestine prevents the colonization by pathogenic bacteria.

Chemical factors (Antimicrobial substances): The barrier defense of skin and mucous membrane are reinforced by the presence of antibacterial substances.

Lysozyme, a hydrolytic enzyme, found in the mucus secretions and in tears, is able to cleave the peptidoglycan of the bacterial cell wall. Saliva contains antibacterial hydrogen peroxide (H_2O_2). The low pH of stomach and vagina is inimical to most bacteria. Cholera infection occurs more rapidly in association with achlorhydria.

Several substances, possessing antimicrobial property, have been described in blood and tissue. These include:

1. Beta-lysine active against anthrax and related bacilli.
2. Basic polypeptides (leukin from leukocytes and plakin from platelets).
3. Lactic acid found in the muscle tissue and in the inflammatory zone.
4. Lactoperoxidase in the milk.
5. Virus inhibiting substances (antiviral substances) inhibit viral hemagglutinin.
6. A cysteine-rich peptide called defensins secreted by a variety of cells (epithelial cells, neutrophils, macrophages) in the skin and mucous membrane.
7. Other molecules with microbicidal functions include cathelicidin, deoxyribonuclease (DNases) and ribonuclease (RNases).
8. Acute phase proteins (Table 3.1).

In an acute phase of infection, pathogens ingested by macrophages stimulate the synthesis and secretion of several cytokines. Cytokines such as interleukin-1 (IL-1) and IL-6 travel through the blood and cause the liver to synthesize and secrete acute phase proteins into the blood.

Interferons: A method of defence virus infection is the production of interferon (IFN) by cells stimulated by live or killed viruses and certain other inducers. IFN has been shown to be more important than specific antibodies in protection against and recovery from certain acute viral infections.

Immunoglobulin: All classes of immunoglobulins (Ig) have been detected on mucous membranes, but IgA is the most important, because it is present in the greatest amount. IgA is a dimer, linked by secretory piece that not only aids transport, but also renders it resistant to proteolytic enzymes in the secretions. IgA is not involved in complement -mediated killing (classical pathway), but impedes adherence, an essential first step in colonization.

Complement system: The complement is a group of serum proteins that circulate in an inactive state. A variety of specific and non-specific immunologic mechanisms can convert the inactive form of complement proteins into an active form leading to lysis of bacteria, cells and viruses; promotion of phagocytosis (opsonization); triggering of inflammation; secretion of immune-regulatory molecules and clearance of immune complex from the circulation. In the innate immune system, complement can be activated by alternative pathway or via the mannan-binding lectin (MBL) pathway.

Table 3.1 Role of acute phase proteins in innate immunity

Acute phase proteins	Role in resistance
C-reactive protein	Stimulate and modulate inflammations
α1-acid glycoprotein	Improved wound healing
α1-trypsin	Control tissue damage by leukocyte proteins
α1-macroglobulin	Increased granulopoiesis and macrophage activation
Complement	Promotes phagocytosis
Haptoglobin	Ingestion of complexes by macrophages, remove iron source from bacteria
Fibrinogen	Coagulation
Lipopolysaccharide-binding protein (LPS-BP) complex	More powerful activator of macrophages

Cytokines and chemokines: The cytokines are secreted by leukocytes and other cells and are involved in innate immunity, adaptive immunity and inflammation. Cytokines act in an antigen non-specific manner, triggering a wide range of biological activities from chemotaxis to activation of specific cells. Chemokines are subgroups of cytokines of low molecular weight involved in chemotaxis (chemical-induced migration).

Commensal flora: It prevents colonization by pathogens. Alteration of normal resident flora may lead to invasion by extraneous microbes causing serious disease such as staphylococcal and clostridial enterocolitis following antibiotics. Commensals protect the host by various mechanisms:

1. Competition for available food and tissue receptors.
2. Production of toxic substances, such as fatty acids or antagonistic substance such as bacteriocins.
3. Stimulation of antibodies (natural antibody that may cross react with pathogens).
4. Keeping the immune system primed, so that the monocytes bear class II histocompatibility antigens needed for immune response.

Second line of defense

When the first line of defense fails, either because of congenital or acquired defects, then the way to deeper tissue is open to bacteria and the next lines of defense come to play. Ciliary dysfunction associated with respiratory infections is one of the congenital defects. There are many examples of acquired defects, the increasing use of indwelling devices provides niches for bacterial colonization and infection. Bacteria (e.g. *Staphylococcus epidermidis*) grow on these foreign bodies in a biofilm, protect them from host defense.

Cellular factors in innate immunity: Natural defense against the invasion of the blood and tissue is mediated by phagocytic cells. Phagocytosis is the process by which the invading organisms are ingested by phagocytic cells, ingestion being followed by intracellular killing. Many cells are able to ingest the

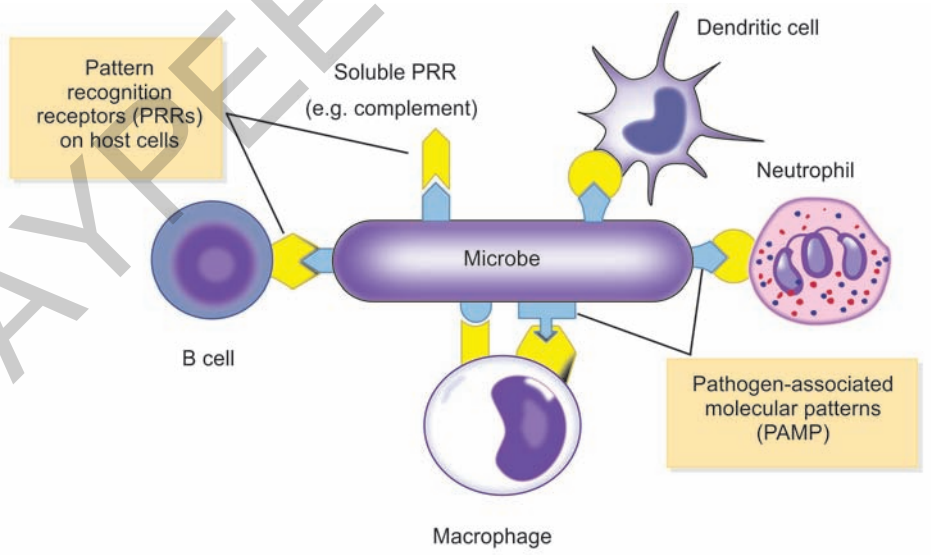


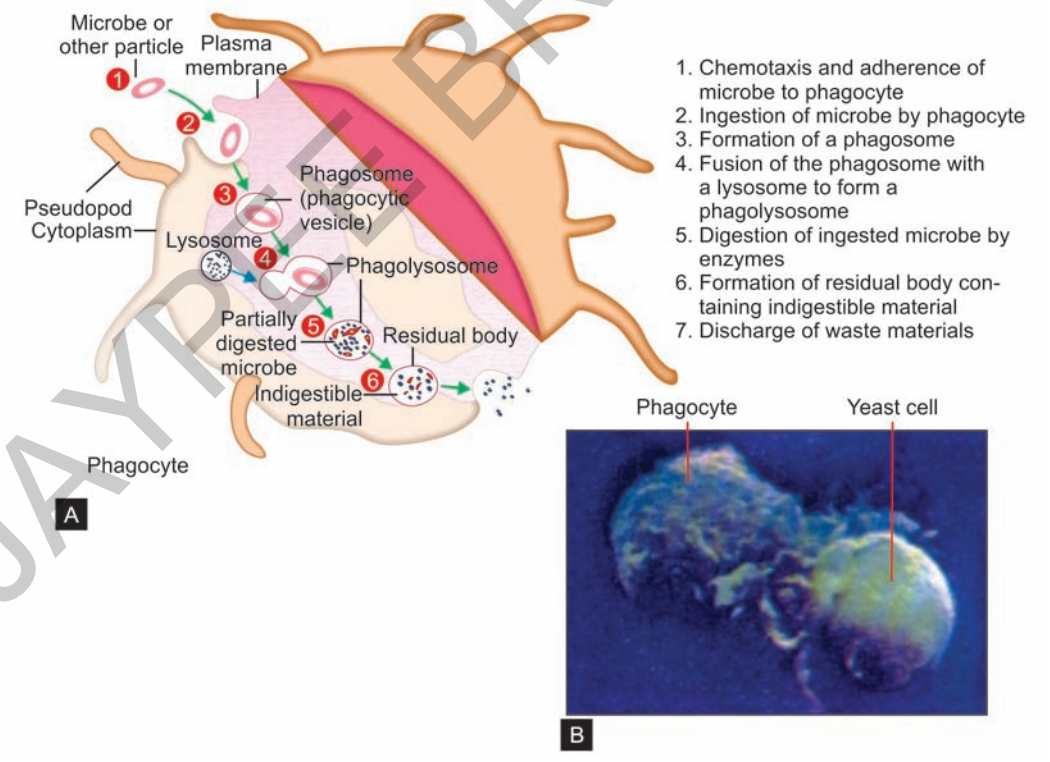
Fig. 3.2: Pattern recognition receptors (PRRs). PRRs detect and bind pathogen-associated molecular patterns (PAMPs).

particles, e.g. endothelial cells, but three cells may be regarded as professional phagocytes. These are neutrophils, macrophages and to a much lesser degree eosinophils. Macrophages consist of histiocytes (wandering ameboid cells found in the tissue), the fixed reticulo-endothelial cells and blood monocytes.

The innate immune system provides a rapid, initial means of defense against infection using genetically programmed receptors that recognize these structural features of microbes that are not found in the host. Such receptors are known as pattern recognition receptors (PRRs), which are found on or in phagocytic cells, which bind to pathogen-associated molecular patterns (PAMPs) (Fig. 3.2). PAMPs are conserved, microbes-specific carbohydrates, proteins, lipids and/or nucleic acid (e.g. lipopolysaccharide, peptidoglycan, etc.). PRRs binding to PAMPs result in phagocytosis and enzymatic degradation of the infectious organisms (Figs 3.3A and B).

Pattern recognition receptors engagement can lead to activation of the host cell and its secretion of antimicrobial substances. PRRs include:

1. Toll-like receptors (TLRs), which signals the synthesis and secretion of cytokines to promote inflammation by recruiting cells.
2. Scavenger receptors that are involved in internalization of bacteria and phagocytosis of host cells that are undergoing apoptosis.
3. Opsonins, the molecules (C3a, IgM), which bind to microbes to facilitate their phagocytosis.



Figs 3.3A and B: Mechanism of phagocytosis in a phagocyte. **A.** Phases of phagocytosis; **B.** Phagocyte engulfing an yeast cell.

The cells under stress, either by infection or by cancerous change, express certain stress molecules (heat shock protein, MICA and MICB on the surface of the cells). These stress signals are detected by various receptors, including some of the TLRs (e.g. TLR2, TLR4) and the killer activation receptors (KARs) on the natural killer (NK) cells. Killer inhibition receptors (KIRs) on NK cells assess major histocompatibility complex class I (MHC I) molecules on the target cell surface. NK cells bring about the death of organisms (viruses) and tumor cells not by intracellular digestion, but by extracellular killing by liberating perforin, a cytolysin after degranulation (Fig. 3.4). The activity of NK cells is greatly increased by exposure to IFNs and cytokines.

Inflammation: Tissue injury, initiated by the entry of pathogens leads to inflammation, which is an important non-specific mechanism of defense. Hence, inflammation acts as a protective phenomenon.

1. Blood flow to the particular part is increased.
2. There is an outpouring of plasma, which dilutes the toxins and enzymes.
3. Chemotactic factors including C5a, histamine, leukotrienes, etc. will attract phagocytic cells to the site. The increased vascular permeability will allow easier access for neutrophils and monocytes. Vasodilation means more cells in the vicinity.

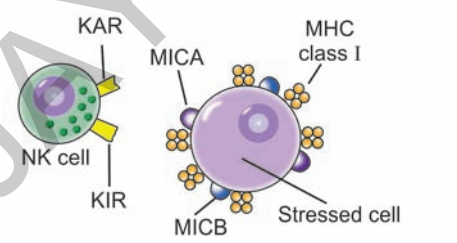


Fig. 3.4: Killer cell activation receptors (KARs) and killer cell inhibition receptors (KIRs) are expressed on NK cells. On nucleated cells, KARs detect stress-related molecule, MICA and MICB, while KIRs detect MHC class I molecules.

4. There is formation of fibrin barrier, which limits the inflammation.
5. There is activation of complement and also the specific defenses.

Fever: A rise of temperature following infection, helps in following ways:

1. Mobilization defenses.
2. Accelerate repairs.
3. Inhibits pathogens.
4. Stimulates the production of IFNs and helps in recovery from virus infection.

Therapeutic induction of fever was employed previously for destruction of *T. pallidum*.

The mechanisms of all the innate immunity is given in Figure 3.5.

Acquired Immunity

The resistance an individual acquires during life is called acquired immunity.

Active Immunity (Adaptive Immunity)

Active immunity or adaptive immunity is capable of recognizing and selectively eliminating specific foreign microorganisms and molecules, i.e. tumor antigens, transplanted antigens, etc. This involves the active functioning of the individual's immune apparatus, either in producing antibody or creating immune-competent cells for cell-mediated immunity (CMI). Active immunity sets in only after a latent period, which the immunological machinery needs for its functioning. Once developed the active immunity is long lasting. When the individual is facing the same antigen subsequently, there is no latent or lag phase and the immune response is prompt, powerful and prolonged (Table 3.2).

In contrast to the innate immune response, which recognize the common molecular patterns such as PAMPs in potential invaders, the adaptive immune system resorts to a highly different approach with a very large repertoire of specific antigen receptors that

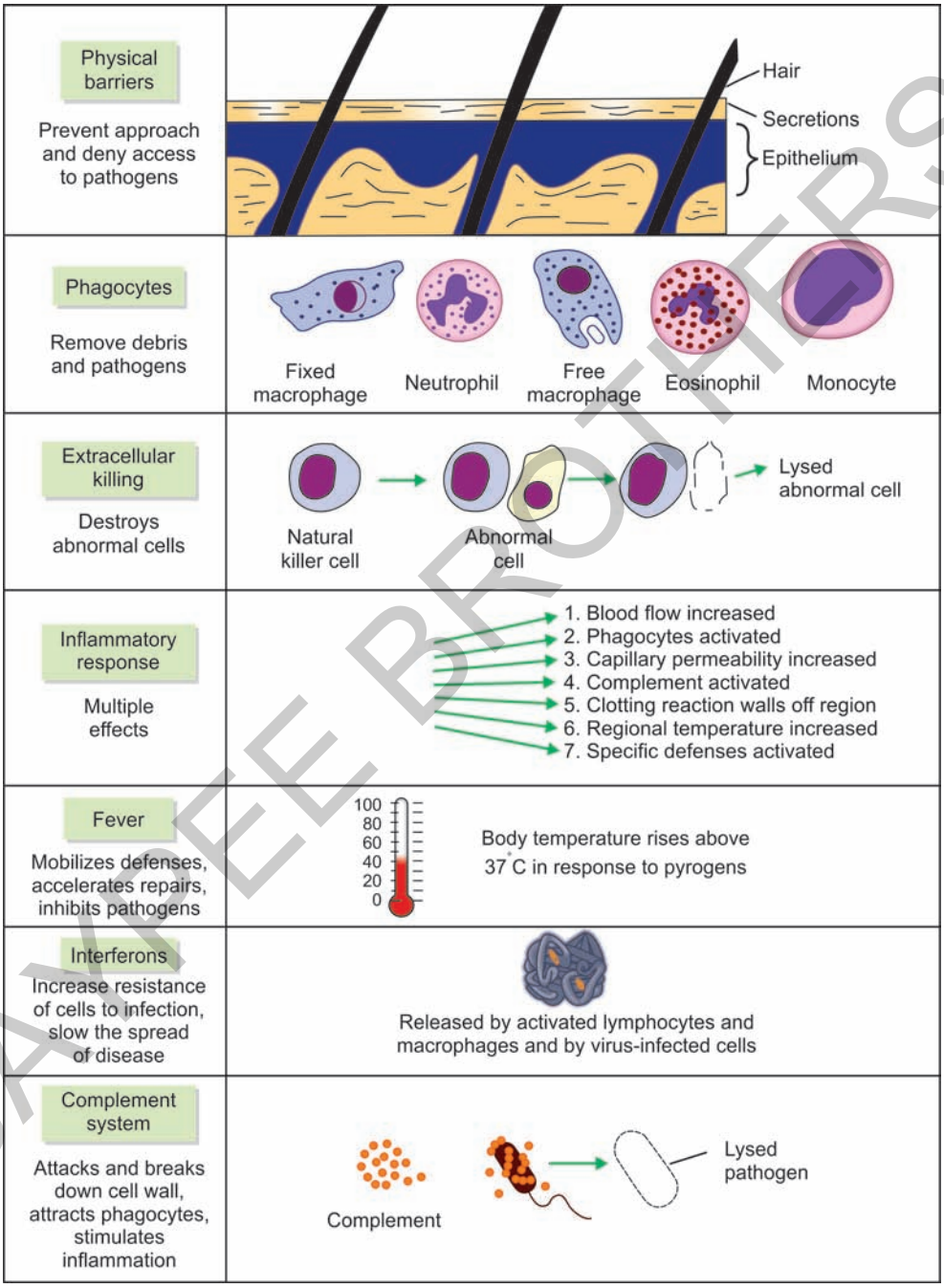


Fig. 3.5: Mechanism of innate immunity

can recognize virtually, any component of the foreign invader.

Adaptive immunity focuses on four important characteristic features. They are:

1. Antigenic specificity.
2. Diversity.
3. Immunological memory.
4. Self/non-self recognition.

The antigenic specificity of the immune system permits it to distinguish minor difference among antigens. The antibodies can distinguish between two protein molecules that differ in only a single amino acid. The immune system is capable of generating tremendous diversity in its recognition molecules, permitting to recognize vast arrays of unique structures on foreign antigens. Once the immune system recognized and responded to an antigen, it exhibits immunological memory to recognize the same antigen, subsequently and react in a heightened manner (Refer Table 3.2). Finally, the immune system, normally responds to foreign antigens, indicating that it is capable of distinguishing self from non-self.

The adaptive immunity is not independent of innate immunity. They interact constantly. The phagocytic cells crucial to nonspecific immune responses are intimately involved in igniting the specific immune response. Conversely various soluble factors produced during specific immune response have been shown to augment the activity of these phagocytic cells.

Naturally acquired active immunity: This type of immunity is obtained when a person is exposed to antigens in the course of daily life. Once acquired, the immunity lasts for rest of its life such as in measles and chickenpox. For other diseases, especially in intestinal diseases, the immunity is short lasting. Subclinical infections can also conform immunity as that occurs in tuberculosis. Adults have natural immunity against polio after repeated subclinical infections.

In syphilis, malaria and few other diseases, a special type of immunity is observed known as infection immunity (premunition). The immunity to reinfection lasts as long as the original infection persists.

Table 3.2 Comparison of active and passive immunity

	Active	Passive
Mechanism	Produced actively by the host immune system	Obtained passively, no participation
Induction	Induced by infection (clinical and subclinical) Induced by immunogens, vaccines	Conferred by ready-made antibody
Durability	Protection is durable and effective	Protection is transient and less effective
Lag phase	Present	No lag phase
Immunological memory	Present, subsequent challenge is more effective	No immunological memory, hence no secondary response
Negative phase	May occur	No negative phase
Application to immune deficient subjects	Not applicable	Effective in immune deficient hosts

Artificially acquired active immunity: This type of immunity results from vaccination or immunization. Vaccinations may be inactivated bacterial toxins (toxoids), killed microorganisms, live but attenuated microorganisms or parts of microorganisms such as capsules.

These substances can no longer cause disease, but can stimulate immune response.

Examples of vaccines are as follows:

1. Bacterial vaccines
   - Live and attenuated → Bacille Calmette-Guérin (BCG) for tuberculosis
   - Killed → Typhoid-paratyphoid A and B vaccine (TAB) for enteric fever
     Taboral vaccine for typhoid (oral vaccines)
     Cholera vaccine
     Pertussis vaccine
     Bacterial capsule polysaccharides
     - *Haemophilus influenzae*
     - *Pneumococcus*
     - *Meningococcus.*
   - Subunit → Vi polysaccharide for typhoid (Vi virulence)
   - Bacterial products → Toxoids for diphtheria tetanus
   - Bacterial products and killed bacteria → Triple vaccine.
2. Viral vaccines
   - Live and attenuated → Smallpox
     Oral polio (Sabin)
     Influenza
     Measles, mumps, rubella (MMR)
   - Killed (inactivated) → Injectable Polio (Salk)
     Yellow fever
     Influenza
     Rabies
   - Subunit → Hepatitis B vaccine.

Live vaccines initiate an infection without causing any injury or diseases. The immunity lasts for several years. Booster dose may or may not be required. Live oral (polio) or nasal spray (influenza) vaccines provide local immunity.

Killed vaccines are generally less immunogenic than the live vaccines and the immunity lasts only for a short period. Therefore, they are administered repeatedly. Killed vaccines are given parenterally.

Passive Immunity

Passive immunity is resistance exhibited by the host, when ready-made antibodies or defensive cells are introduced into the body. This form of protection is passive, because the individuals own immune system does not make antibodies or defensive cells against the disease producing agents or toxins.

Naturally acquired passive immunity: This type of immunity involves natural transfer of antibodies from mother to her infant and also from mother to fetus. Certain antibodies (IgA) are passed from the mother to her nursing infants in breast milk, especially in the first secretion called colostrum. The immunity in infants last as long as baby feeds on breast milk.

During pregnancy, some of the maternal antibodies are also transferred through placenta to the fetus. If the mother is immune to diphtheria, rubella or polio, the newborn

will be temporarily immune to these diseases as well.

Artificially acquired passive immunity: This type of immunity involves the introduction of antibodies into the body. These antibodies come from animal or person, who is already immune to the disease. They are:

1. Hyperimmune sera of animal or human origin. Common examples are antitetanus serum (ATS), antidiphtheria serum (ADS), anti-gas-gangrene serum (AGS), antisnake venom, etc.
2. Convalescent sera from patients very recently recovered from measles, rubella, etc.
3. Pooled gamma globulin serum against common infectious diseases.
4. Human gamma globulin is also used in the treatment of immunodeficiency diseases.

Indication of Passive Immunization

1. For providing immediate and temporary protection in a non-immune host.
2. Treatment of some infections.
3. Antilymphocytic serum (ALS) may be given for suppression of lymphocytes in transplantation surgery.
4. Passive immunization may also be employed to suppress active immunity, when the latter may be injurious. The commonest example is the use of Rh immunoglobulin during delivery to prevent immune response to rhesus factor in Rh-negative women with Rh-positive babies.
5. Combined immunization.

At times, both active and passive immunization is given together. Ideally, it is employed to provide immediate protection to non-immune individual with a tetanus-prone wound. Tetanus immunoglobulin (TIG) will provide immediate passive immunity and toxoid will initiate active immunity.

ADOPTIVE IMMUNITY

Adoptive immunity is a special type of immunization, where the immunocompetent cells are injected. At times, instead of whole lymphocytes, an extract of lymphocytes (transfer factor of Lawrence) may be introduced as a therapeutic procedure in certain disease, such as lepromatous leprosy, immunodeficiency diseases such as Wiskott-Aldrich syndrome, disseminated malignancy, etc. Recent studies indicate that the adoptive T cell transfer is done, preferably, in the treatment of virus-related diseases in particular, cytomegalovirus (CMV) infection and Epstein-Barr virus (EBV) infection—associated lymphoproliferative diseases (LPDs).

Local Immunity

The mucosal immune system is composed of the lymphoid tissues that are associated with the mucosal surface of the gastrointestinal, respiratory and the urogenital tracts. These include mucosal-related Igs. The system involves production of mucosal-related Ig that is IgA (secretory immunoglobulin). The primary function of the mucosal immune system is to provide defense to the host at mucosal surface, locally. Optimal host defense at the mucosal surface depends on both intact mucosal immue responses and non-immunologic protective functions such as residential bacterial flora, mucosal motor activity (peristalsis; ciliary function), mucus secretion that create barrier between potential pathogens and epithelial surfaces and innate immunity factors (lactoferin, lactoperoxidase and lysozyme).

The concept local immunity has gained importance in the treatment of infections, which are either localized or where it is operative in combating infection at the site of primary entry of pathogens.

The Sabin vaccine (for poliomyelitis) is administered orally to promote local IgA

(secretory IgA) production in the intestinal tract. This prevents entry and multiplication of the organism.

Influenza (live-attenuated) vaccine is most effective when given in nasal spray. Research to find out an oral vaccine against cholera is on the process.

Herd Immunity

Herd immunity refers to an overall immunity exhibited by a community, which is relevant in the control of epidemic diseases. When the herd immunity is satisfactory, epidemic does not occur. When it is less, the prevention of epidemic can be done by mass immunization.

There are limits to the herd immunity. However, if a significant number of unprotected individuals become infected, the infection could spread rapidly through the unprotected members of population. In the course of that rapid replication, new mutant forms might arise that could evade the immune response and produce diseases in vaccinated individuals as well.

STUDY QUESTIONS

Essay Questions

1. Define innate immunity. Explain various innate immune mechanisms.
2. Classify immunity. Describe acquired immunity with examples.

Short Notes

1. Artificially acquired active immunity.
2. Killed vaccines.
3. Live-attenuated vaccines.
4. Oral vaccines.
5. Herd immunity.
6. Premunition.
7. Pattern recognition receptors (PRRs).

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Textbook of IMMUNOLOGY

Salient Features

- Presents an updated and complete textbook in all aspects
- Covers history of immunology, host-microbe relationship and disease process, basic immunology, diagnostic immunology, immune response, immunopathological disorders, immunohematology, immunological tolerance, transplantation immunology, tumor immunology, immunity against bacteria, parasites, viruses, fungi, etc. and other interesting topics such as immunodeficiency states with special reference to HIV, the details of the cytokines in relation to classification, biological functions, cytokine receptors, cytokine antagonists, cytokine-related diseases and prospects, etc.
- Includes illustrative graphics, colored diagrams, flow charts and tables as and where required to make the text lucid and interesting
- Study questions at the end of each chapter—perfect for classroom learning and preparation for tests
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- Helpful for doctors, researchers, teachers and students.

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Professor Mohanty has authored a textbook and has published more than 40 research papers in peer-reviewed national and international journals. He is recipient of many applause, commendation and award as orator, moderator and chairperson in a number of symposia and seminars at the state and national levels. He was nominated as a member to the research advisory board of Kamineni Education Society at Hyderabad, Andhra Pradesh. He was actively associated with several state and national level programs such as AP, AIDS CON, RNTCP, Leprosy Control, etc.

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