Immune response in human pathology: infections caused by bacteria, viruses, fungi, and parasites

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Infections

In the middle of the 19th century, it became clear that micro-organisms could cause disease. Effective treatment, however, was not possible at that time; prevention and spread of infectious diseases depended solely on proper hygienic means. At the beginning of the 20th century, passive and active vaccination procedures were developed against a number of these pathogenic micro-organisms in order to prevent the diseases in question (rabies, diphtheria, tetanus, etc.) and due to the discovery of antimicrobial chemicals (Ehrlich) and antibiotics (Fleming), the threat of infectious diseases seemed to be minimized. Large-scale vaccination programs against childhood diseases (diphtheria, whooping cough and polio) started in the early fifties, giving hope to finally eradicate these diseases from the planet. This approach was successful for smallpox (1980); however, new infectious diseases emerged (e.g., Legionella, HIV, Helicobacter, SARS, etc.). New vaccines and antibiotics are needed. Furthermore, due to the intensive medical treatment with antibiotics and immunosuppressive drugs, hospital infections are a growing problem. Bacteria hitherto deemed harmless are causing opportunistic infections in immunocompromised patients. The pathogens develop multiple resistances to antibiotics and sometimes no effective antibiotics are available to treat those patients.

To make the story evermore serious, man is surrounded and populated by a large number of different non-pathogenic micro-organisms. In the normal – healthy – situation, there is a balance between the offensive capabilities of micro-organisms and the defences of the human body. The body's defences are based on vital non-specific and specific immunological defence mechanisms. An infection means that the microorganism has succeeded in penetrating those lines of defence, signaling a partial or complete breakdown of the body's defence system.

Natural resistance

The body's first line of defence comprises the intact cell layers of skin and mucous membrane, which form a physical barrier. The skin's low pH level and bactericidal fatty acids enhance the protection provided by this physical barrier. The defence in the respiratory tract and the gastrointestinal tract is mucous, the 'ciliary elevator' of the epithelium, and the motility of the small intestine. The presence of normal microbial flora (colonization resistance) in the intestine also plays a role in protection against colonization.

The most important humoral natural resistance factors are complement, lysozyme, INTERFERON, and a number of CYTOKINES. Lysozyme, which is found in almost all body fluids, degrades sections of the cell wall of Gram-positive and – in combination with complement – Gram-negative bacteria. This causes the otherwise sturdy cell wall to leak and the bacterium to burst.

Interferons are glycoproteins which may inhibit the replication of viruses. Within several hours after the onset of a virus infection, INTERFERONS are produced in the infected cell and help protect the neighbouring unaffected cells against infection. This protection is brief, but high concentrations of INTERFERONS are produced at a time when the primary immunological response is relatively ineffective.

CYTOKINES, such as IL-2 (INTERLEUKIN-2), GM-CSF (granulocyte-macrophage colony-stimulating factor), and TNF-α (TUMOR NECROSIS FACTOR α), stimulate non-specifically the proliferation, maturation, and

BOX 1. CLASSIFICATION OF MICRO-ORGANISMS

Classification of bacteria by

Genotypic characteristics:	chromosomal DNA fragment analysis, nucleic acid sequence analysis, probes
Phenotypic characteristics:	morphology, biotyping, serotyping, antibiotic resistance
Analytic characteristics:	cell-wall analysis, lipid and protein analysis, enzyme typing (catalase)
Gram staining positive or negative	
Aerobic, anaerobic:	fermentation of different sugars

Naming and classification of viruses according to

Structure:	size, morphology (naked, enveloped), nucleic acid (RNA, DNA)
Molecular aspects:	mode of replication, assembly and budding
Disease:	encephalitis, hepatitis
Means of transmission:	droplets, water, blood, insects
Host range:	animal, plant, bacteria

Classification of fungi according to

Structure:	macroscopic morphology of hyphae (mycelium)
	microscopic morphology of hyphae, conidophores and conidia (spores) shape and size
Cell features:	nucleus, cytosol, plasmalemma (cell membrane which contains cholesterol), physiology, staining properties
Sexual characteristics:	sexual and /or asexual reproduction, extended dikaryotic phase, basidium formation
Genotypic characteristics:	chromosomal DNA fragment analysis, nucleic acid sequence analysis, probes

Diagnosing of parasites by

Macroscopic examination

Concentration of cysts and eggs by microscopic examination

Serological diagnosis: antibody response

Detection of parasite by serology and by nucleic acid hybridization: probes and amplification techniques

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function of the cells involved in defence (see Chapter A.4).

Innate immune cells recognize microbes by TOLL-LIKE RECEPTORS (see section Pathogenesis of shock), giving rise to the above production of CYTOKINES in the early phase of the response.

Micro-organisms that succeed in penetrating the first line of defence are ingested, killed, and degraded by phagocytic cells (leukocytes, MONOCYTES, MACROPHAGES), which are attracted to a microbial infection through chemotaxis. The ingestion by phagocytic cells of the micro-organism is enhanced by serum proteins (opsonins), such as ANTIBODIES and the C3b component of complement, for which these phagocytes have a receptor. After ingestion, the particle is surrounded by the membrane of the phagocyte, forming a vacuole known as a PHAGOSOME . The PHAGOSOME then fuses with some of the countless lysosomes in the phagocyte, thus allowing the lysosomal microbicidal agents and enzymes to do their

BOX 2. SOME EXAMPLES OF IMPORTANT HUMAN PATHOGENS

	Species	Disease / location	Treatment / prevention
Bacterium	*Streptococcus pneumoniae*	pneumonia / meningitis	antibiotics / vaccination
	Mycobacterium tuberculosis	lung tuberculosis	antibiotics
	Vibrio cholerae	severe diarrhea	antibiotics / liquid suppletion / sanitation
	Staphylococcus aureus MRSA	wound infection / hospital infection	antibiotics, MRSA not sensitive for standard antibiotics, difficult to treat
	Neisseria meningitidis	meningitis	antibiotics / vaccination
	Bacillus anthracis	systemic infection (sepsis)	antibiotics as early as possible
	Corynebacterium diphteriae	throat / heart	anti-serum, vaccination
	Campylobacter jejuni	intestinal infections	hygiene, especially food (chicken)
	Helicobacter pylori	gastritis, ulcer	antibiotics
DNA Virus	Poxviridae	smallpox	vaccination, eradication
	Herpesviridae	Herpes genitalis	anti-viral agents
	Papavoviridae	warts and cervical carcinoma	surgery
	Hepadnaviridae	hepatitis B	vaccination
RNA Virus	Orthomyxoviridae	influenza	vaccination
	Coronaviridae	SARS	unknown
	Retroviridae	AIDS	anti-viral agents
	Caliciviridae	gastro-intestinal infection	sanitation, hygiene
Parasites	*Plasmodium* species	malaria	prophylactic medication, anti-malarial drugs
	Giardia species	intestinal tract	hygiene
	Trypanosoma cruzi	sleeping sickness	anti-parasitic agents

work. In the case of leukocytes, the formation of toxic oxygen radicals greatly contributes to the killing and elimination of the ingested micro-organism (Fig. 1) (see Chapter A.6).

A special role in cellular natural resistance is reserved for the NK (natural killer) cells, which display considerable cytotoxic activity against virus-infected cells. This NK activity is stimulated by INTER-FERONS and, at a very early stage in the infection, serves to reinforce the non-specific defence mechanism.

Specific resistance

In the specific immune response, elements of the natural defence mechanism are directed against a specific enemy. Depending on the micro-organism, either the cellular defence mechanism (tuberculosis) or the humoral antibody-dependent defence mechanism (influenza) is of primary importance. In many cases, a joint cellular and humoral
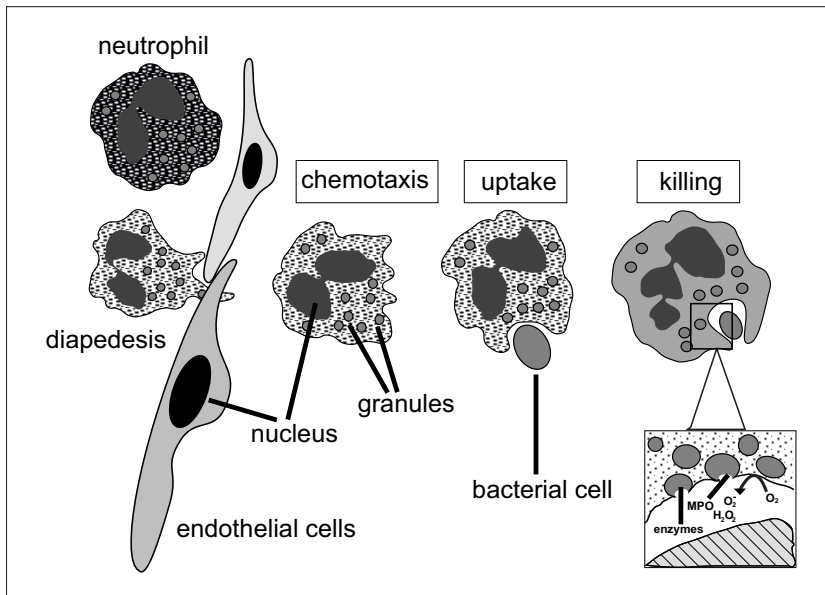
FIGURE 1
Schematic representation of the progressive steps of phagocytic endocytosis.

response is needed to provide an effective defence (typhus).

Both T LYMPHOCYTES and MACROPHAGES play a role in cellular defence. During the first contact with an antigen, MACROPHAGES process the antigen and present its protein fragments (T-cell epitopes) to T cells, which then proliferate and remain present for years in the body as memory cells. When a second encounter occurs, T cells produce lymphokines, which activate the MACROPHAGES. These activated MACROPHAGES grow larger, produce more and better degrading enzymes, and are now able to eliminate micro-organisms which otherwise would have survived intracellularly (tuberculosis, typhoid fever). MACROPHAGES from non-immune animals are not able to eliminate these micro-organisms.

Five different classes of ANTIBODIES can be distinguished in man, namely, IgG, IgA, IgM, IgD, and IgE. They differ from one another in size, charge, amino acid composition, and glycosylation (see Chapter A.3, C.2). In principle, the structure of the ANTIBODIES is the same, i.e., 2 heavy and 2 light chains: it is the variable part of these chains which recognizes the micro-organism. The biological function (see below) is determined by the constant part (Fc) of the heavy chain. With the exception of IgD, all these ANTIBODIES are important in antimicrobial activity.

- IgA, which is found in all external secretions, reacts with the surface of micro-organisms, preventing them from adhering to sensitive cells and mucous membranes.
- IgG neutralizes microbial toxins.
- IgG, IgM, and C3b serve as opsonins, which promote PHAGOCYTOSIS.
- IgG, IgM, and to a lesser extent IgA activate the COMPLEMENT SYSTEM after binding to the micro-organism. Activation products C3a and C5a ensure that the phagocytes are attracted to the inflammatory response.
- IgG and IgM, in combination with complement and lysozyme, have a lytic effect on bacteria and enveloped viruses.
- IgG and IgM inhibit the mobility of micro-organisms by attaching specifically to the flagellum. When this happens the chance of PHAGOCYTOSIS increases and the chance of spreading of disease decreases.
- IgG, together with the killer or K cells, can eliminate infected host cells which carry viral or other foreign ANTIGENS on their surface.

- IgE is of importance in parasite infections. At the site of the infection, mast cells, bearing specific IgE, release large quantities of vasoactive amines, which cause the contraction of smooth muscle tissue and increase the permeability of the blood vessels. In the intestine, this results in worms being detached and eliminated.

Defence against bacteria, viruses, fungi, and parasites

Several non-invasive bacteria, i.e., those that do not invade the body, cause disease through the production of exotoxins (tetanus, diphtheria, cholera). The immune system neutralizes the toxin with the aid of ANTIBODIES (IgG, IgM). If the individual has not been inoculated, the toxin will act on certain cells in the body directly through a receptor. This bond is very strong (i.e., has a high affinity), and is difficult to break by the administration of ANTIBODIES. In practice, if there are clinical symptoms of the disease, then large doses of antitoxins must be administered. If one is trying to prevent the development of the disease, then the presence of small quantities of specific ANTIBODIES (IgG) is sufficient.

The adherence of bacteria to cells is effectively blocked by IgA. Oral vaccination against cholera, for example, is aimed at obtaining sufficient specific IgA in the intestine, so that no colonization of this bacterium can take place, and the cholera toxin can no longer adhere to its receptor.

In general, defence against invasive bacteria is provided by ANTIBODIES (IgG, IgM) that are directed against bacterial surface antigens. In many cases, these bacteria have a capsule which interferes with effective PHAGOCYTOSIS. ANTIBODIES against these capsule ANTIGENS neutralize the interference, with subsequent elimination of the bacteria by phagocytes. ANTIBODIES (IgM, IgG, IgA) in combined action with complement kill bacteria by producing holes in the cell wall of the bacterium.

Although intracellular bacteria (tuberculosis, leprosy, listeriosis, brucellosis, legionellosis, and salmonellosis) are ingested by MACROPHAGES, they are able to survive and multiply. In these cases, cellular immu-
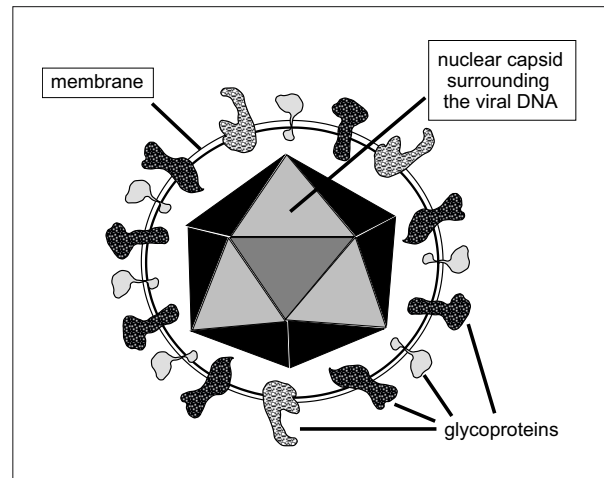

FIGURE 2
*Schematic illustration of an enveloped virus (*Herpes simplex *virus).*

nity alone provides the defence, since ANTIBODIES are not effective. Only activated MACROPHAGES are capable of killing and degrading these bacteria.

ANTIBODIES neutralize viruses (Fig. 2) directly and/or indirectly by destroying infected cells that carry the virus antigen on their surface. The mechanisms of this defence resemble those of humoral defence against bacterial surfaces. The antibody-dependent cellular cytotoxicity reaction is specific for the defence against viruses. Cells which carry on the surface an antigen encoded by the virus are attacked by cytotoxic K cells, bearing ANTIBODIES which fit the antigen on the target cell (K cells have Fc receptors for IgG).

Not only humoral, but also cellular immunity plays an important role in virus infections. People with a genetic T-cell deficiency are highly susceptible to virus infections. In cellular defence, it is primarily the virus-infected cells which are attacked and eliminated. Cytotoxic T cells recognize MHC-1-presented T-cell epitopes on the surface of virus-infected cells and kill them.

The fungi responsible for human diseases can be divided into two major groups on the basis of their growth forms or on the type of infection they cause. Pathogens exist as branched filamentous forms or as

yeasts, although some show both growth forms. The filamentous types (*Trichophyton*) form a 'mycelium'. In asexual reproduction, the fungus is dispersed by means of spores; the spores are a common cause of infection after inhalation. In yeast-like types (*Cryptococcus*), the characteristic form is the single cell, which reproduces by division or budding. Dimorphic types (*Histoplasma*) form a mycelium outside, but occur as yeast cells inside the body. *Candida* shows the reverse condition and forms a mycelium within the body.

In superficial mycoses, the fungus grows on the body surface, for example skin, hair, and nails (*Epidermophyton*, *Trichophyton*), the disease is mild, and the pathogen is spread by direct contact. In deep mycoses (*Aspergillus*, *Candida*, *Cryptococcus*, *Histoplasma*), internal organs are involved and the disease can be life-threatening and is often the result of opportunistic growth in individuals with impaired immunocompetence.

Many of the fungi that cause disease are free-living organisms and are acquired by inhalation or by entry through wounds. Some exist as part of the normal body flora (*Candida*) and are innocuous unless the body's defences are compromised in some way. The filamentous forms grow extracellularly, while yeasts can survive and multiply within phagocytic cells. Neutrophils kill yeasts by means of both intra- and extracellular factors. Some yeasts (*Cryptococcus neoformans*) form a thick polysaccharide capsule in order to prevent phagocytic uptake. In addition, many cell-wall components of yeasts cause suppression of cell-mediated immune responses. The role of humoral and cellular immunity in controlling infections caused by fungi is not yet well defined, but cellular immunity is the cornerstone of host defence against (some) fungal infections. As a consequence, HIV infection, which affects the cellular arm of the immune system, results in previously uncommon infections such as those caused by *C. neoformans*.

The immunological defence systems against *parasites* are considerably more complex than those against bacteria and viruses. This is due to various factors. In the first place, each parasite has its own life cycle, consisting of various stages with specific antigen compositions. Moreover, parasites are able to avoid the host defence system (mimicry), to combat it (immunosuppression), or to mislead it (antigenic variation). Both humoral and cellular immunity are important for the defence against parasites growing intercellularly, as we have seen in the case of bacteria and viruses. ANTIBODY concentrations (IgM, IgG, IgE) are often elevated. IgE also plays a special role in the removal of parasites (especially worm infections) from the intestine (see above).

Pathogenesis of shock

In Gram-negative (Fig. 3) bacterial infections, the interaction between bacterial endotoxin and various host-cell systems has been implicated in the pathogenesis of septic shock. In particular, the release of TNF-α (also called cachectin) and INTERLEUKIN-1 (IL-1), after the activation of host cells by endotoxin, induces hemodynamic shock.

Several lines of evidence support the current hypothesis that the monocyte-macrophage is the principal cellular mediator of endotoxicity. First, C3H/HeJ mice carrying a single gene defect are nonresponsive to lipopolysaccharide (LPS). The transfer of MACROPHAGES of a closely related LPS-sensitive strain makes the mice responsive. Second, when the host is challenged with endotoxin, soluble factors are produced by MACROPHAGES that mediate fever and an acute-phase response. These factors include the proinflammatory CYTOKINES, IL-1, IL-6, IL-8, and TNF-α. Together, TNF-α and IL-1 stimulate endothelial cells to produce and express proteins on their membrane that have adhesive properties for leukocytes, promoting the migration and passage of POLYMORPHONUCLEAR LEUKOCYTES (PMNs) from blood vessels through the endothelial layer, leading to PMN influx into the tissue. Adhesion molecules that mediate the binding of PMNs appear on the endothelium after an inflammatory stimulus, followed by molecules that are specific for adhesion of MONOCYTES or LYMPHOCYTES, which may be why neutrophils enter before mononuclear cells. Molecules that are currently known to be involved in leukocyte-endothelium interactions belong to three structural groups: the IMMUNOGLOBULIN gene superfamily, the INTEGRIN family, and the selectin family.

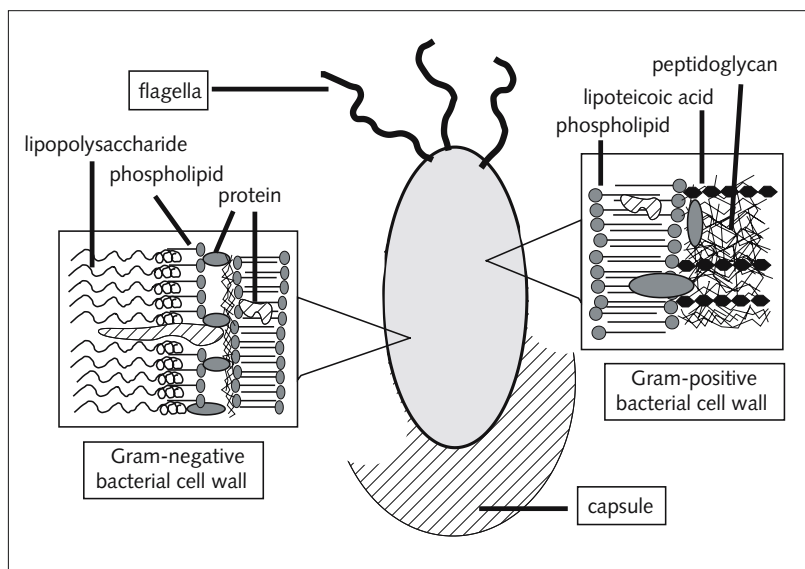Concomitant with cytokine release, LPS induces the activation of PMNs, MACROPHAGES, and many other

FIGURE 3

Schematic illustration of the cell envelope of a gram-negative and a gram-positive bacterium.

cells, resulting in the release of toxic oxygen radicals, which lead to tissue damage. At the same time, membrane-associated phospholipases are activated and products of the arachidonic-acid cascade are released through the cyclooxygenase and/or lipooxygenase pathways (see Chapter A.6). Platelet-activating factor (PAF) is also generated, partly in response to the same signals. All these products contribute to a generalized inflammatory state with influx of PMNs, capillary-leak syndrome, disturbances in blood coagulation, and myocardial suppression.

Endotoxin and TNF-α also produce multiple abnormalities in coagulation and fibrinolysis, leading to microvascular clotting and diffuse intravascular coagulation. They also induce endothelial cells to produce plasminogen activator and IL-6, which is an important modulator of the production of acute-phase proteins by the liver. Interestingly, despite having important structural differences, TNF-α and IL-1 have multiple overlapping and few distinct biological activities, act synergistically, and mimic the whole spectrum of toxicity caused by LPS (see Chapter A.4). IL-8 is an important chemoattractant and activator of neutrophils and is crucial in the early stages of inflammation.

Infusion of endotoxin in healthy humans leads to an early and transient increase in plasma levels of TNF-α (detectable after 30 min, peaking after 90–120 min, and undetectable after 4–6 h), which coincides with the development of clinical symptoms and pathophysiological responses encountered in Gram-negative septicemia. TNF-α, IL-1, IL-6, and IL-8 levels are also increased in patients with sepsis syndrome, with high levels of these CYTOKINES being correlated with severity of disease.

All these observations support the concept that endotoxin largely acts by initiating an inflammatory response through the activation of MONOCYTES-MACROPHAGES and the subsequent release of CYTOKINES. It also activates the COMPLEMENT SYSTEM (leading to the generation of C5a, which induces aggregation of PMNs and pulmonary vasoconstriction) and factor XII of the intrinsic coagulation pathway (Hageman factor). Finally, it induces the release of ENDORPHINS, which are also involved in the complex interactions of the inflammatory response in endotoxic septic shock.

Gram-positive bacteria are frequently and increasingly cultured from blood obtained from patients in shock. Unlike the pathophysiology of shock caused by Gram-negative bacteria, not much is
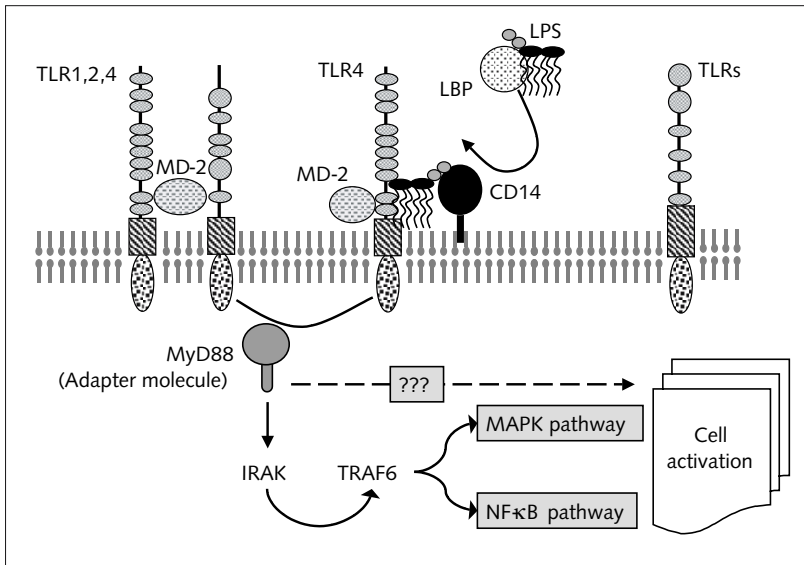
Figure 4
Schematic illustration of cell activation through toll-like receptors (TLRs).

known about the sequence of events that controls the signaling of MONOCYTES and MACROPHAGES that leads to the release of CYTOKINES. Cell-wall components, such as peptidoglycan and teichoic acid, are clearly important in the activation of these cells. Exotoxins, however, may also play a role in the pathogenesis of Gram-positive bacterial shock.

CD14 is a cell surface glycoprotein that functions as a binding receptor for LPS. However its membrane anchoring by a glycosylphosphatidyl inositol (GPI) linkage suggests little signaling and suggests the existence of additional coreceptors. Recent studies indicate that innate immune cells recognize conserved pathogen-associated molecular patterns (PAMPs), including LPS, through TOLL-LIKE RECEPTORS (TLRs) (Fig. 4). This family of proteins, that resemble the antimicrobial Toll proteins of *Drosophila*, has been identified in humans and mice. TLR4 was identified as the missing link in LPS-induced cell signal transduction and responsiveness that is associated with MD-2 and CD14. The TLR family members are coupled to a signaling adapter protein (MyD88) and form differential dimers that may explain the discrete responses to TLR ligands such as lipoprotens, heat shock proteins, unmethylated CpG DNA, viral dsRNA and bacterial flagellin. Intracellular signaling involves several kinases depending on the TLRs

involved and includes the MAP kinase and NF-κB pathways leading to a cellular response. Recently other protein families have been identified via genetic screening that also participate in direct recognition of pathogens. A new protein was found to be involved in resistance to Gram-positive bacterial infections and recognizes the cell wall component peptidoglycan.

Human immunodeficiency virus infection

The human immunodeficiency virus (HIV) is a retrovirus that infects cells bearing the CD4 antigen, such as T-helper cells (TH), MACROPHAGES, and DENDRITIC CELLS. The CD4 molecule, together with other receptor molecules, like chemokine receptor 5, acts as a binding site for the gp120 envelope glycoprotein of the virus. In an attempt to respond to HIV ANTIGENS and concomitant secondary microbial infections, these cells are activated, thus inducing the replication of HIV in the infected CD4 T cells, which are finally destroyed. In contrast, HIV-1 infection of MACRO-PHAGES is self-sustained and results in an inexorable growth of chronic active inflammatory processes in
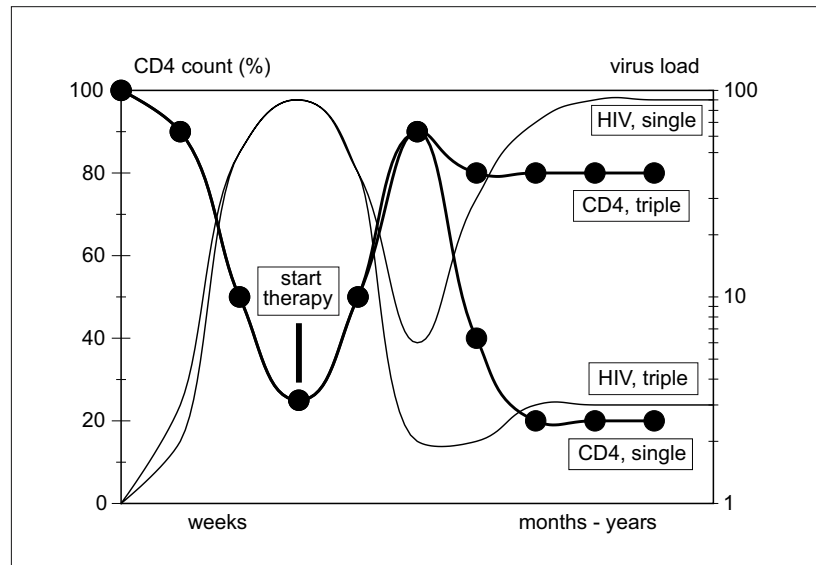
FIGURE 5

The effect of single and triple therapy on viral load and CD4 cells over time in HIV-infected individuals.

many tissue compartments including the central nervous system. Infected cells bear the fusion protein gp41 and may therefore fuse with other infected cells. This helps the virus to spread and accounts for the multinucleated cells seen in lymph nodes and brain. As a result of the decreased numbers of CD4-positive T-helper cells and defects in antigen presentation, depressed immune responses in these patients are observed. During the progression of the disease, opportunistic infections by otherwise harmless micro-organisms can occur. These include *Candida albicans* oesophagitis, mucocutaneous herpes simplex, toxoplasma in the central nervous system, and pneumonia caused by toxoplasma and *Pneumocystis carinii*; Kaposi's sarcoma also occurs frequently in these patients. This has been linked to the presence of a previously unknown type of Herpes virus (HHV-8). This immune deficiency syndrome is called 'acquired immune deficiency syndrome' (AIDS). It has been suggested that infected MONOCYTES/MACROPHAGES carry the HIV virus into the brain where it replicates in microglia and infiltrating MACROPHAGES. As a consequence many AIDS patients develop cognitive and motor brain impairments. However, the picture is complicated by the various persistent infections already present in these patients, which give rise to their own pathology in the brain. These

include *Toxoplasma gondii*, *Cryptococcus neoformans* and JC virus.

So far a cure for HIV infection has not been achieved. The main effort in the prevention of HIV infection lies in mass public education programmes. Treatment of infected individuals is possible but expensive. At this moment a triple therapy is being prescribed in the Western countries (two reverse transcriptase inhibitors and one protease inhibitor, Fig. 5), each of which interfere with specific steps in the process of HIV replication. One major problem that has arisen is the increasing resistance to these drugs. Blocking of the chemokine receptor 5, a recently described co-receptor on CD4 cells for HIV, may be an alternative treatment for infected persons. This notion is supported by a recent finding that a homozygous defect in this chemokine receptor accounts for resistance of multiple-exposed individuals to HIV-1 infection.

Vaccines and vaccinations

Pasteur and Koch triggered the stormy development of vaccines (anthrax, rabies, cholera) at the end of the 19th century. While Pasteur remained faithful to the principle of attenuated micro-organisms in

preparing his vaccines, Koch employed killed germs (cholera) as a vaccine. Since diphtheria and tetanus cause disease by means of toxins, the next logical step in the development of vaccines was the use of detoxified toxins to induce protection against these diseases (diphtheria, Von Behring and tetanus, Kitasato). Von Behring and Kitasato were the first to demonstrate that the source of the protective activity induced by vaccines was present in blood serum. Von Behring was also the first to prove that protective immunity could be passed on via serum. The development of new vaccines had its ups (yellow fever) and downs (tuberculosis). With the arrival of antibiotics, all work on new bacterial vaccines was suspended or severely curtailed, although some researchers continued to work on viral vaccines, such as rubella, measles, polio, and mumps.

Since it has proved difficult to consistently develop new antibiotics to combat antibiotic-resistant bacteria, interest in vaccines has gradually increased over the last 15 years (see Chapter C.1). Today, thanks to new insights into the immune system and modern molecular biological and chemical techniques of analysis and synthesis, it is possible to produce well-defined vaccines. These contain only those determinants of the pathogenic microorganism which induce protection (epitopes). These epitopes are usually short peptide or oligosaccharide chains, which can be produced synthetically or by means of recombinant DNA techniques. The immunogenicity of these products can be enhanced by coupling them to a carrier (tetanus toxoid, liposomes) and/or by adding an adjuvant (a substance which strengthens the immune response non-specifically). The recombinant DNA technique can also be used to obtain attenuated strains of micro-organisms, which are fully immunogenic and thus provide protection, but which are no longer virulent. One example of this is the development of a new cholera vaccine based on a bacterium which has all the characteristics of a virulent strain, except the toxin. The bacterium has retained all its adherence factors, which allow it to adhere to the intestinal mucosa; the length of time it spends in the intestine is sufficient to stimulate the local immune system. The newest trend in vaccinology is immunization by introducing plasmid DNA into the host. Success has been attained by this method for hepatitis B vaccination.

Not only are new vaccines being developed, but it is also possible to heighten natural resistance for longer or shorter periods. Various INTERLEUKINS (IL-2, GM-CSF) and INTERFERONS are being studied in order to use them to combat infectious diseases. Monoclonal ANTIBODIES (ANTIBODIES with one specificity) directed against the endotoxin of Gram-negative bacteria are now being administered to patients with severe Gram-negative sepsis (serum therapy). More work is still necessary, however, to refine this technique, as the therapeutic effect is still limited.

Infections in the new millenium

As outlined above for a number of bacteria and viruses, effective vaccines have been developed and applied worldwide. The eradication of smallpox (*Variola major*) virus in the seventies of the last century was a milestone for the World Health Organization. The next goal of the WHO is to eradicate the poliovirus in the coming years. Major problems to be dealt with are the distribution of these vaccines, the costs involved, the registration and the compliance of the vaccinees and molecular techniques to trace the final bug. Meanwhile new unexpected microbiological threats come into focus. Hospital infections caused by multiple resistant micro-organisms due to the abundant use of antibiotics and exchange of genetic material between micro-organisms impose major problems on patients and healthcare workers. New antibiotics and/or vaccines should be developed and new strategies employed to contain these infections. Due to crowding and high mobility of the world population, old and new pathogens, e.g., influenza and SARS, threaten our society. On top of this terrorists might intentionally use micro-organisms (Smallpox, Anthrax, Plague etc.), or bacterial toxins (Botulism) to cause death and disease in humans or animals in a civilian setting. The recognition that an event was caused by a biological weapon presents a severe challenge to be prepared for such an attack, especially for medical care providers and public health officials. Strategies to combat bioterrorism have to be worked out but with

the experience of 100 years of combating micro-organisms with hygiene measures, vaccination, antibiotic and anti-viral treatment, there must be a way out.

Summary

Despite the introduction of effective health measurements, vaccination and antimicrobial therapy infectious diseases continue to threaten human life. The reasons are numerous and diverse: antibiotic resistance, hospital-invading pathogens, new emerging infectious diseases, bioterrorism, biological warfare. This chapter is an introduction to several aspects of infectious diseases viewed from the host as well as from the pathogen (bacterium, virus and parasite). Furthermore the basic principles of INNATE and ADAPTIVE IMMUNE RESPONSES, especially in debilitated patients, are described. Detailed information is given on the pathogenesis of septic shock, AIDS and vaccination strategies.

Acknowledgments

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Recommended websites

Scientific Research:
American Society for Microbiologists: *http://www.asm.org*
American Association of Immunology: *http://www.aai.org*
European Federation of Immunological Societies: *http://www.efis.org*
Federation of European Microbiological Societies: *http://www.fems-microbiology.org*
National Library of Medicine: *http://www.ncbi.nlm.nih.gov*

Outbreaks of Infectious Diseases:
Centers for Disease Control and Prevention: *http://www.cdc.gov*
International Society for Infectious Diseases: *http://www.isid.org*
Daily update: *http://www.promedmail.org*
World Health Organization: *http://www.who.int*
(All accessed March 2005)