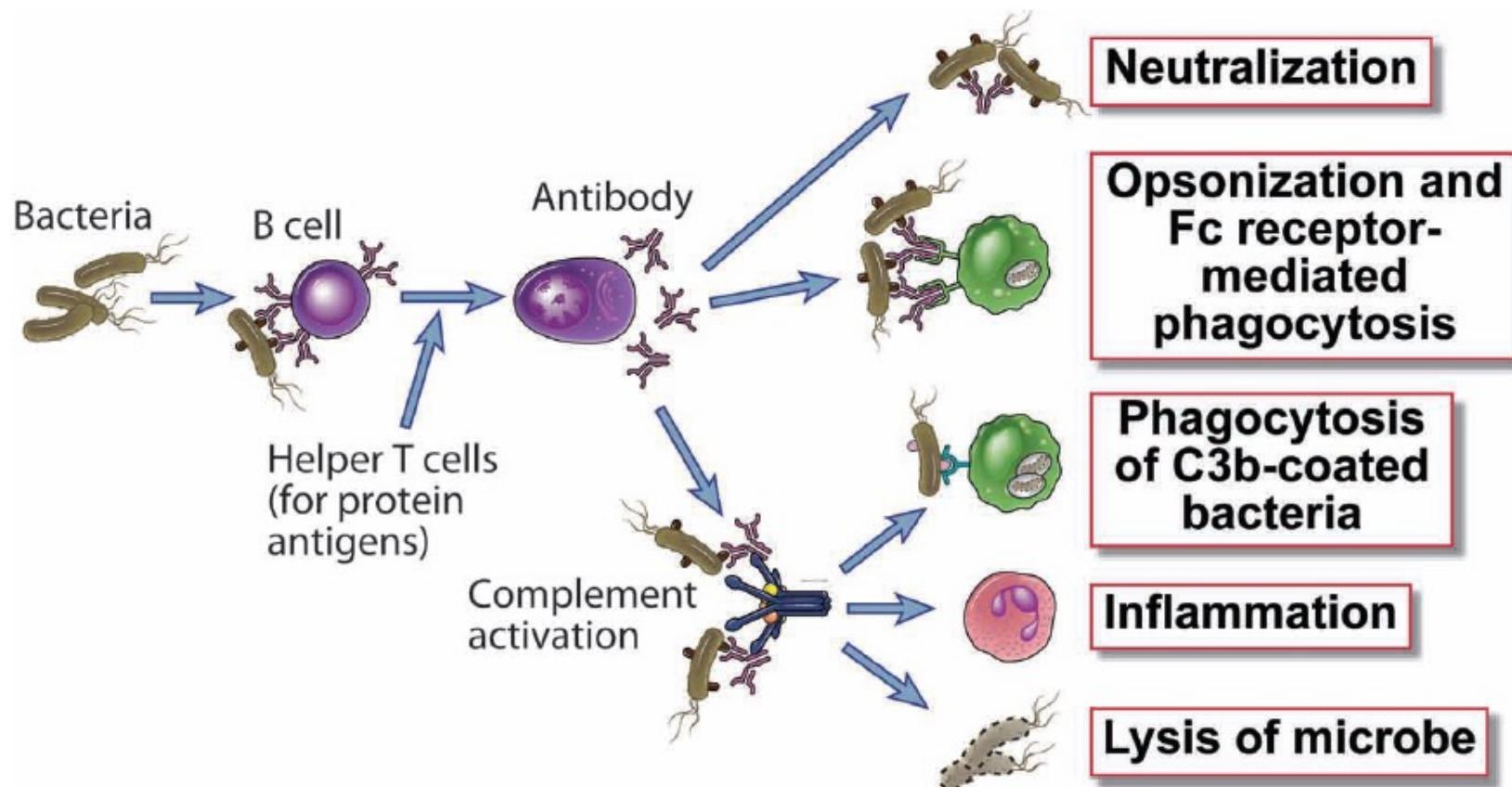
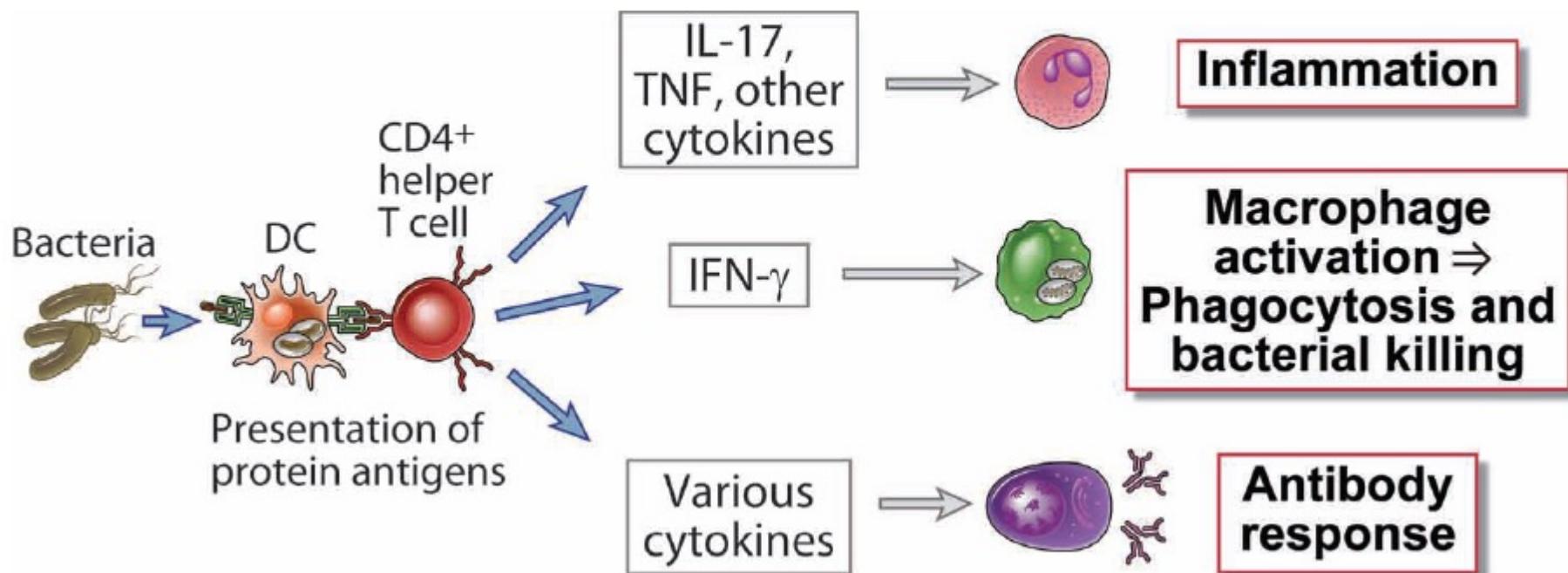


17 Oct 2023,
BT 304
Lecture 30

Antibody Responses to Extracellular Microbes



T Cell Responses to Extracellular Microbes



Injurious Effects of Immune Responses to Extracellular Bacteria

- Neutrophils and macrophages: local production of reactive oxygen species and release of lysosomal (granule) enzymes
- Cytokines -> acute-phase proteins -> systemic manifestations of the infection (see Chapter 4)
- Septic shock: disseminated infection with circulatory collapse and disseminated intravascular coagulation.
 - Cytokine storm: TNF, IL-6, and IL-1 (also IFN- γ , IL-12)
 - associated with defective immune responses, perhaps related to depletion or suppression of T cells, resulting in unchecked microbial spread.
- Disease producing antibodies
 - sequelae of streptococcal infections of the throat or skin (weeks or even months after the infections are controlled)
 - Rheumatic fever: cross-reactive anti-M protein antibodies-> cardiac inflammation
 - Poststreptococcal glomerulonephritis: immune-complexes with bacterial antigen
- Activation of T cells by superantigen
 - Staphylococcal enterotoxin B (SEB)

Activation of T cells by Bacterial Superantigen

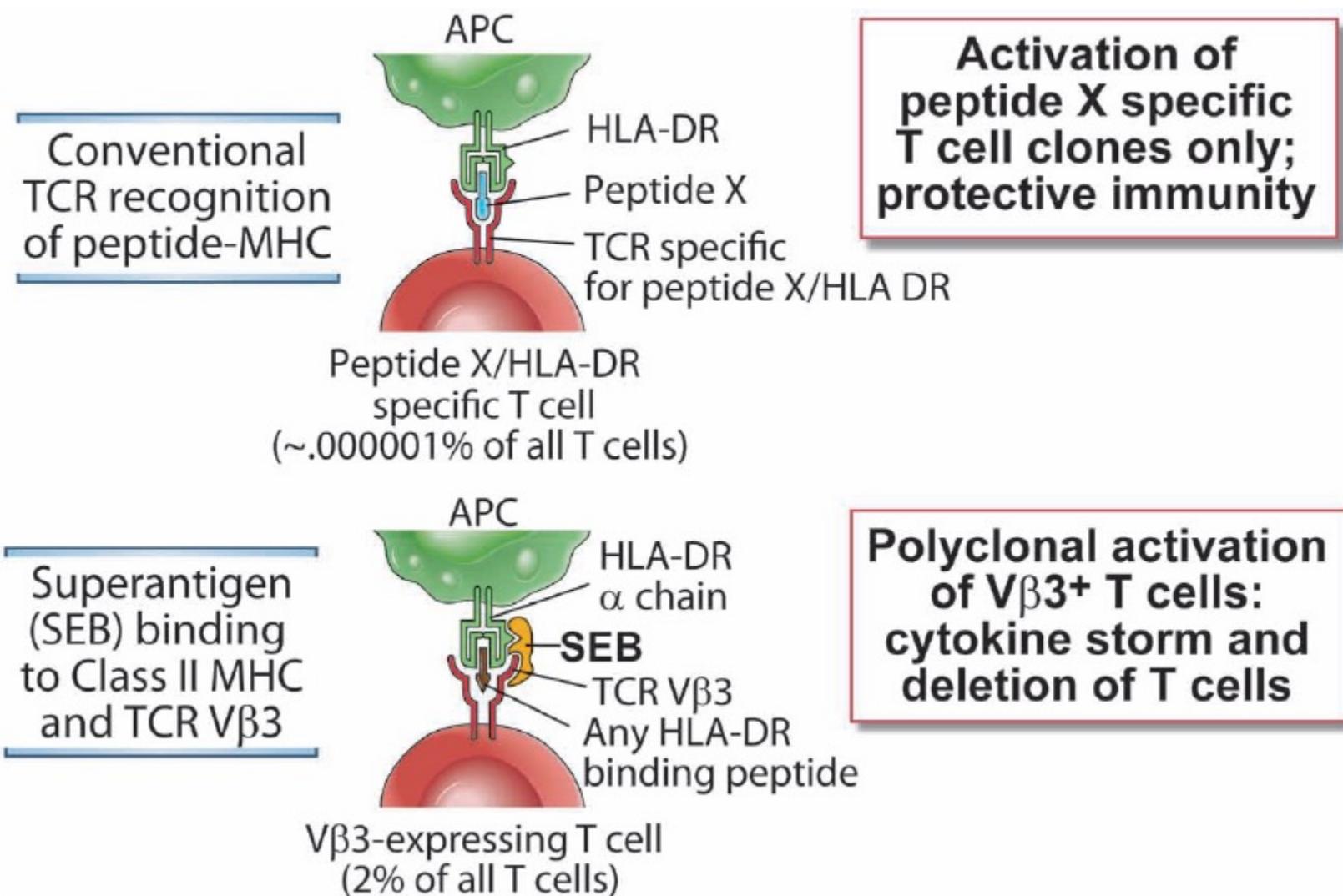


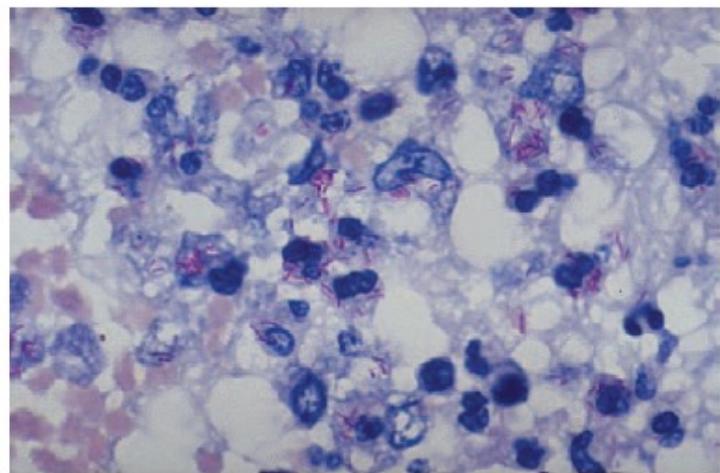
Fig. 15-2

Immune Evasion by Extracellular Bacteria

- Resistance to innate immunity
 - blockade of phagocytosis (polysaccharide rich capsules) (*Pneumococcus*)
 - inhibition of complement or inactivation of complement products (capsule sialic acid inhibits alternative pathway)
 - scavenging reactive oxygen species (Catalase+ *Staphylococci*)
- Resistance to adaptive immunity
 - genetic variation of surface antigens (pilin) (*Neisseria gonorrhoeae*, *Escherichia coli*, *Salmonella typhimurium*)
 - variation in glycosidases -> alterations in surface LPS (*Haemophilus influenzae*)

Immunity to Intracellular Bacteria

- facultative intracellular bacteria:
ability to survive and even to replicate within phagocytes
- inaccessible to circulating antibodies
- elimination requires the mechanisms of cell-mediated immunity
- immune responses often lead to injury



Mycobacterium tuberculosis (acid fast stain)
<http://library.med.utah.edu>

Microbe	Examples of Human Diseases	Mechanisms of Pathogenicity
Mycobacteria	Tuberculosis, leprosy	Macrophage activation resulting in granulomatous inflammation and tissue destruction
<i>Listeria monocytogenes</i>	Listeriosis	Listeriolysin damages cell membranes
<i>Legionella pneumophila</i>	Legionnaires' disease	Cytotoxin lyses cells and causes lung injury and inflammation

7

Table 15-1

Innate responses to intracellular bacteria

- Phagocytes (neutrophils and macrophages)
 - phagocytosis, but resistant to degradation within phagocytes
 - phagocyte activation: TLRs and NOD-like receptor (NLR) family
- NK cells
 - NK cell activation: by NK cell-activating ligands on infected cells, by IL-12 and IL-15 (produced by dendritic cells and macrophages)
 - NK cells produce IFN- γ => activates macrophages and promotes killing of the phagocytosed bacteria

Immunity to Intracellular Bacteria

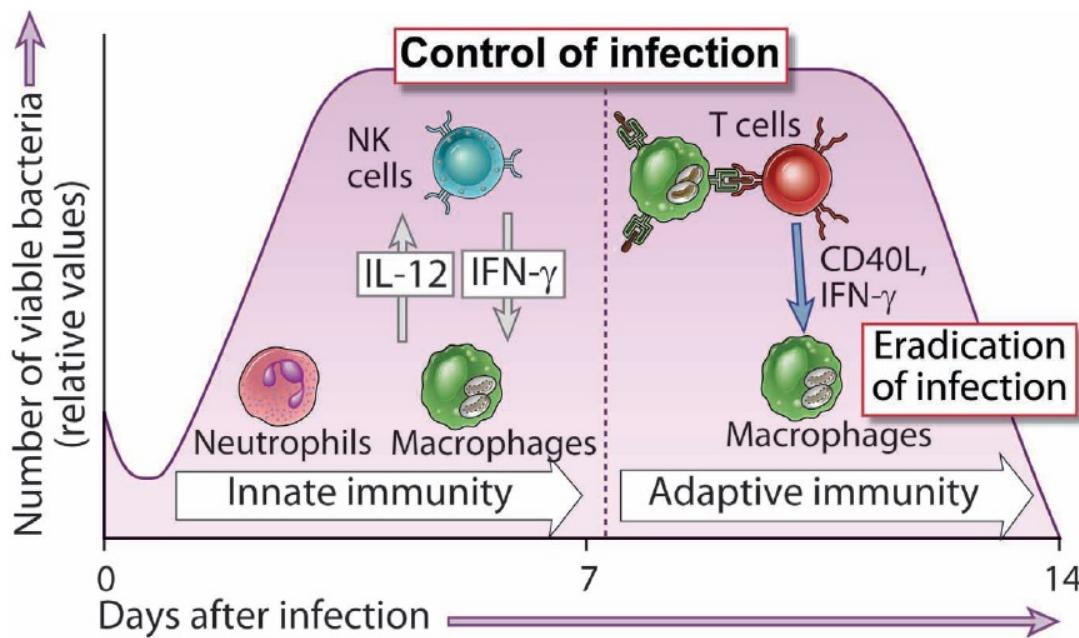


Fig. 15-3

FIGURE 15-3 Innate and adaptive immunity to intracellular bacteria. The innate immune response to intracellular bacteria consists of phagocytes and NK cells, interactions among which are mediated by cytokines (IL-12 and IFN- γ). The typical adaptive immune response to these microbes is cell-mediated immunity, in which T cells activate phagocytes to eliminate the microbes. Innate immunity may control bacterial growth, but elimination of the bacteria requires adaptive immunity. These principles are based largely on analysis of *Listeria monocytogenes* infection in mice; the numbers of viable bacteria shown on the y-axis are relative values of bacterial colonies that can be grown from the tissues of infected mice. (Data from Unanue ER. Studies in listeriosis show the strong symbiosis between the innate cellular system and the T-cell response. Immunological Reviews 158: 11-25, 1997.)

Adaptive Immunity to Intracellular Bacteria

- CD4+ helper T cells
 - bacterial peptides presented by MHC class II molecules
 - CD4+ T cells differentiate into T_H1 effectors under the influence of IL-12
 - CD4+ T cells recruit phagocytes
 - CD4+ T cells express CD40 ligand and secrete IFN- γ
 - activation of macrophages (ROS, NO, lysosomal enzymes)
 - production of antibody isotypes (e.g., IgG2a in mice) that activate complement and opsonize bacteria for phagocytosis
- CD8+ cytotoxic T lymphocytes (CTLs)
 - bacteria escape from phagosomes and enter the cytoplasm of infected cells => MHC class I presentation to CTLs
=> CTLs kill infected cells

T Cell Responses to Intracellular Microbes

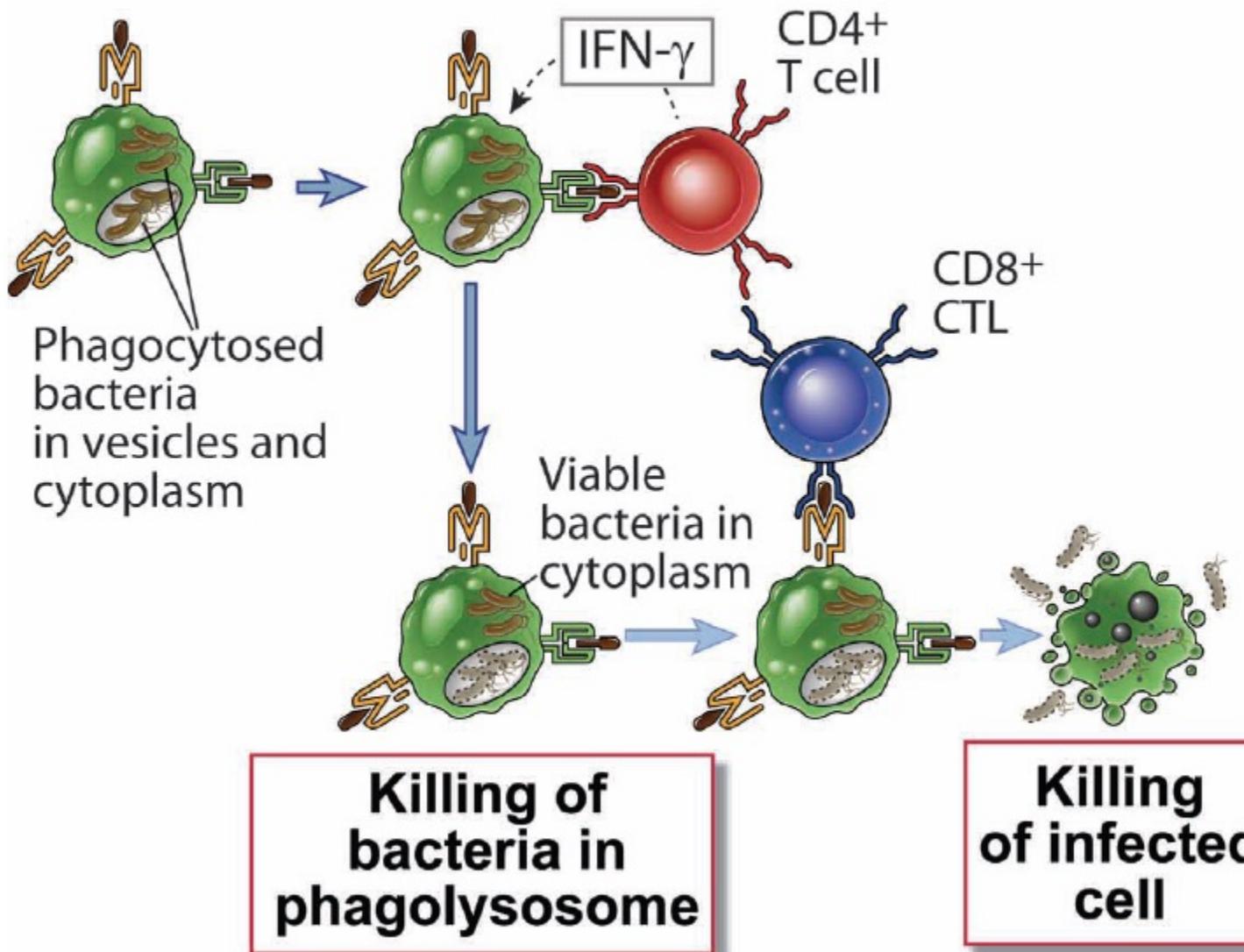
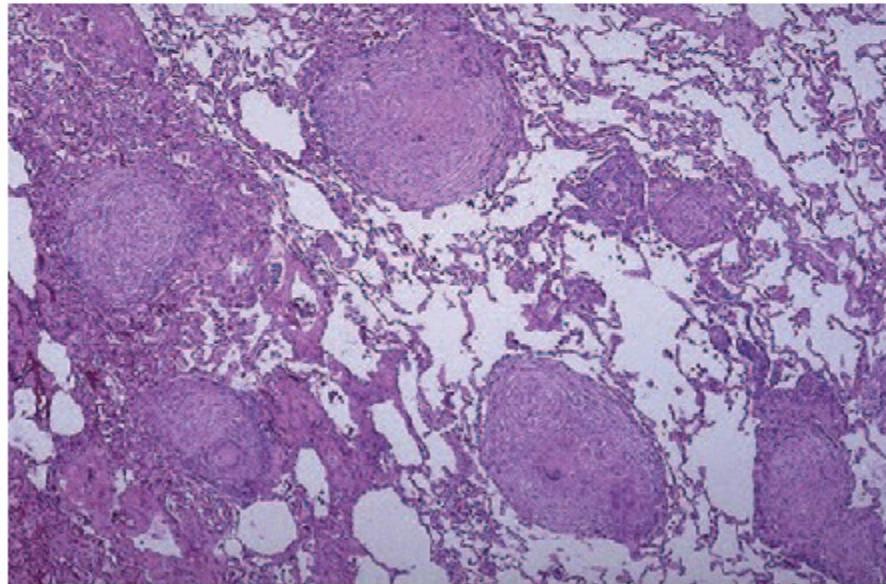


Fig. 15-4

Adaptive responses to intracellular bacteria

The histologic hallmark of infection with some intracellular bacteria is **granulomatous inflammation**. This type of inflammatory reaction may serve to localize and prevent spread of the microbes, but it is also associated with severe functional impairment caused by tissue necrosis and fibrosis.



<http://library.med.utah.edu/>



Tuberculosis

- Mycobacterium tuberculosis: intracellular bacterium => granulomatous inflammation
- Primary infection:
 - multiply slowly in the lungs and cause only mild inflammation
 - infection is contained by alveolar macrophages (and probably DCs)
 - over 90% of infected patients remain asymptomatic, but bacteria survive in the lungs
- Macrophage migrate to draining lymph nodes
 - 6 to 8 weeks after infection
 - activation of CD4+ T cells, also CD8+ T cells
 - produce IFN- γ => macrophage activation, enhanced killing of phagocytosed bacilli
 - TNF produced by T cells and macrophages => local inflammation and macrophage activation
 - T cell reaction: adequate to control bacterial spread but M. tuberculosis is capable of surviving within macrophages
- Continuing T cell activation leads to the formation of granulomas
 - attempt to wall off the bacteria
 - often associated with central necrosis, called caseous necrosis, which is caused by macrophage products such as lysosomal enzymes and reactive oxygen species
 - Necrotizing granulomas and the fibrosis (scarring): that accompanies granulomatous inflammation are the principal causes of tissue injury and clinical disease in tuberculosis.
- Bacilli may survive for many years and are contained without any pathologic consequences but may be reactivated at any time, especially if the immune response becomes unable to control the infection.

Role of T Cell Cytokines in Infections (1)

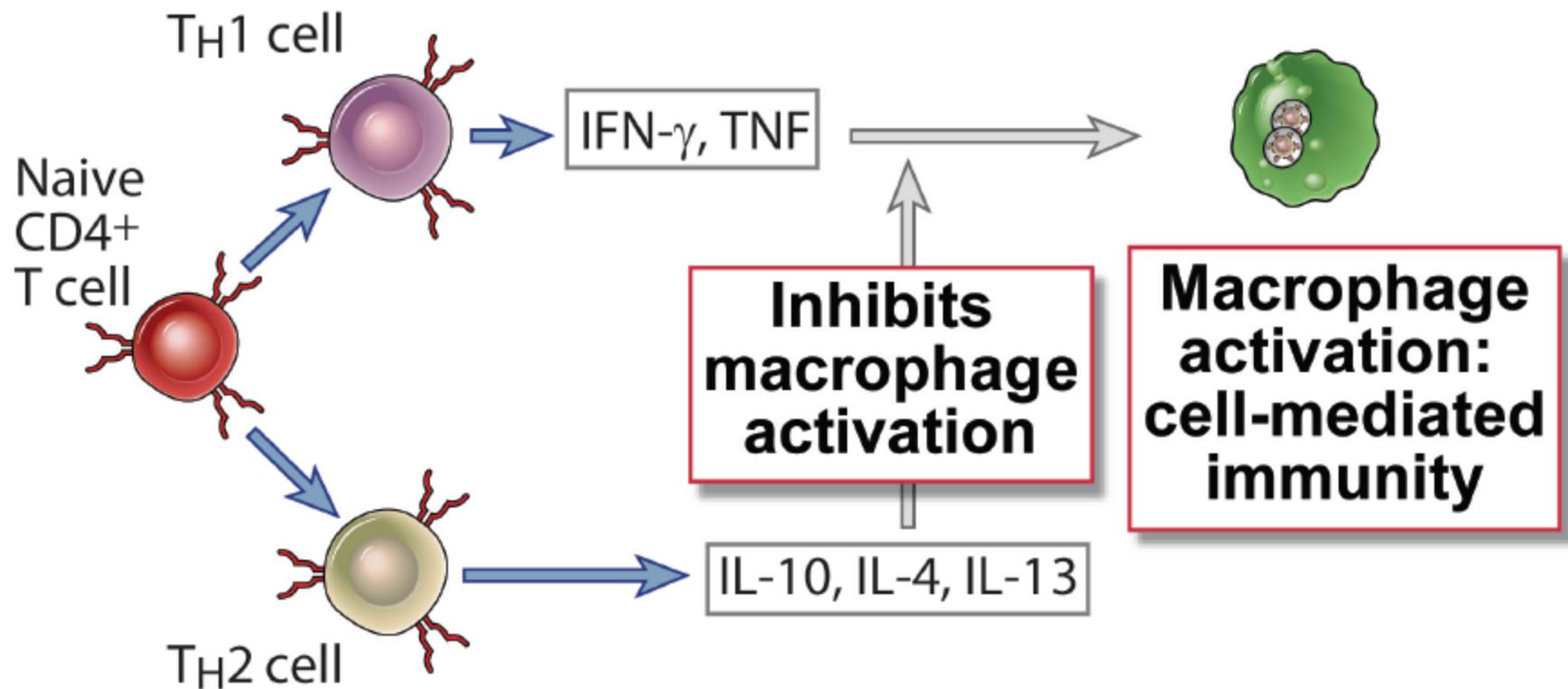


Fig. 15-5A

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Immune Evasion by Intracellular Bacteria

- Resistance to elimination by phagocytes
 - inhibiting phagolysosome fusion (*Mycobacterium tuberculosis*, *Legionella pneumophila*)
 - escaping into the cytosol (*Listeria monocytogenes*)
 - directly scavenging or inactivating microbicidal substances (*Mycobacterium leprae*)
- Resistance to adaptive immunity
 - strength of T cell-stimulated antimicrobial mechanisms of macrophages

Fungal infections (mycoses)

- Fungal infections (mycoses)
 - important causes of morbidity and mortality in humans
 - Endemic or opportunistic
 - Compromised immunity is the most important predisposing factor for clinically significant fungal infections
- Different fungi infect humans and may live in extracellular tissues and within phagocytes => combinations of the responses to extracellular and intracellular bacteria



Aspergillus fumigatus
<http://library.med.utah.edu>

Microbe	Examples of Human Diseases	Mechanisms of Pathogenicity
<i>Candida albicans</i>	Candidiasis	Unknown; binds complement proteins
<i>Aspergillus fumigatus</i>	Aspergillosis	Invasion and thrombosis of blood vessels causing ischemic necrosis and cell injury
<i>Histoplasma capsulatum</i>	Histoplasmosis	Lung infection caused by granulomatous inflammation

Conditions leading to opportunistic fungal infections

Although fungi are ubiquitous in the environment, they generally colonize tissues and cause infection only when the body's normal defenses or the normal flora are disrupted.

- Disruption of the body's physical, chemical, or physiologic barriers: Intact skin, pH, fatty acids in the skin, and various humoral factors normally prevent fungal infection.
- Immunosuppression (inherited or acquired), particularly loss of CD4 T_H1 responses: opportunistic infections by normal flora (e.g., *Candida albicans*) or increased susceptibility to environmental fungi (e.g., *Aspergillus* species) may result.
- Disruption of normal bacterial flora: use of antibacterial drugs sometimes allows colonization by fungi that otherwise would not establish infection.

Innate Immunity to Fungi

- Neutrophils and macrophages
 - fungicidal substances, such as reactive oxygen species and lysosomal enzymes
 - phagocytose fungi for intracellular killing.
 - Phagocytes and dendritic cells sense fungal organisms by TLRs and lectin-like receptors called dectins

Adaptive Immunity to Fungi

- Cell-mediated adaptive immunity: major mechanism against fungi
 - Virulent strains of *Cryptococcus neoformans* inhibit the production of cytokines such as TNF and IL-12 by macrophages and stimulate production of IL-10, thus inhibiting macrophage activation. CD4+ and CD8+ T cells cooperate to eliminate the yeast forms of *C. neoformans*, which tend to colonize the lungs and brain in immunodeficient hosts.
 - *Histoplasma capsulatum*, a facultative intracellular parasite that lives in macrophages, is eliminated by the same cellular mechanisms that are effective against intracellular bacteria.
 - Many extracellular fungi elicit strong T_H17 responses, which are driven in part by the activation of dendritic cells by fungal glucans binding to dectin-1, a receptor for this fungal polysaccharide, and this results in the production of T_H17 -inducing cytokines (IL-6, IL-23) from the dendritic cells. The T_H17 cells stimulate inflammation, and the recruited neutrophils and monocytes destroy the fungi.
 - *Candida* infections often start at mucosal surfaces, and cell-mediated immunity is believed to prevent spread of the fungi into tissues. T_H1 responses are protective in intracellular fungal infections, such as histoplasmosis, but these responses may elicit granulomatous inflammation, which is an important cause of host tissue injury in these infections.
- Fungi also elicit specific antibody responses that are of protective value

Immunity to Viruses

- obligatory intracellular microorganisms that live inside cells
- cytopathic vs non-cytopathic virus infection

Microbe	Examples of Human Diseases	Mechanisms of Pathogenicity
Polio	Poliomyelitis	Inhibits host cell protein synthesis (tropism for motor neurons in the anterior horn of the spinal cord)
Influenza	Influenza pneumonia	Inhibits host cell protein synthesis (tropism for peripheral nerves)
Rabies	Rabies encephalitis	Inhibits host cell protein synthesis (tropism for ciliated peripheral nerves)
Herpes simplex	Various herpes infections (skin, systemic)	Inhibits host cell protein synthesis; functional impairment of immune cells
Hepatitis B	Viral hepatitis	Host CTL response to infected hepatocytes
Epstein-Barr virus	Infectious mononucleosis; B cell proliferation, lymphomas	Acute infection: cell lysis (tropism for B lymphocytes) Latent infection: stimulates B cell proliferation
Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	Multiple: killing of CD4 ⁺ T cells, functional impairment of immune cells

Table 15-1

Immune Responses Against Viruses

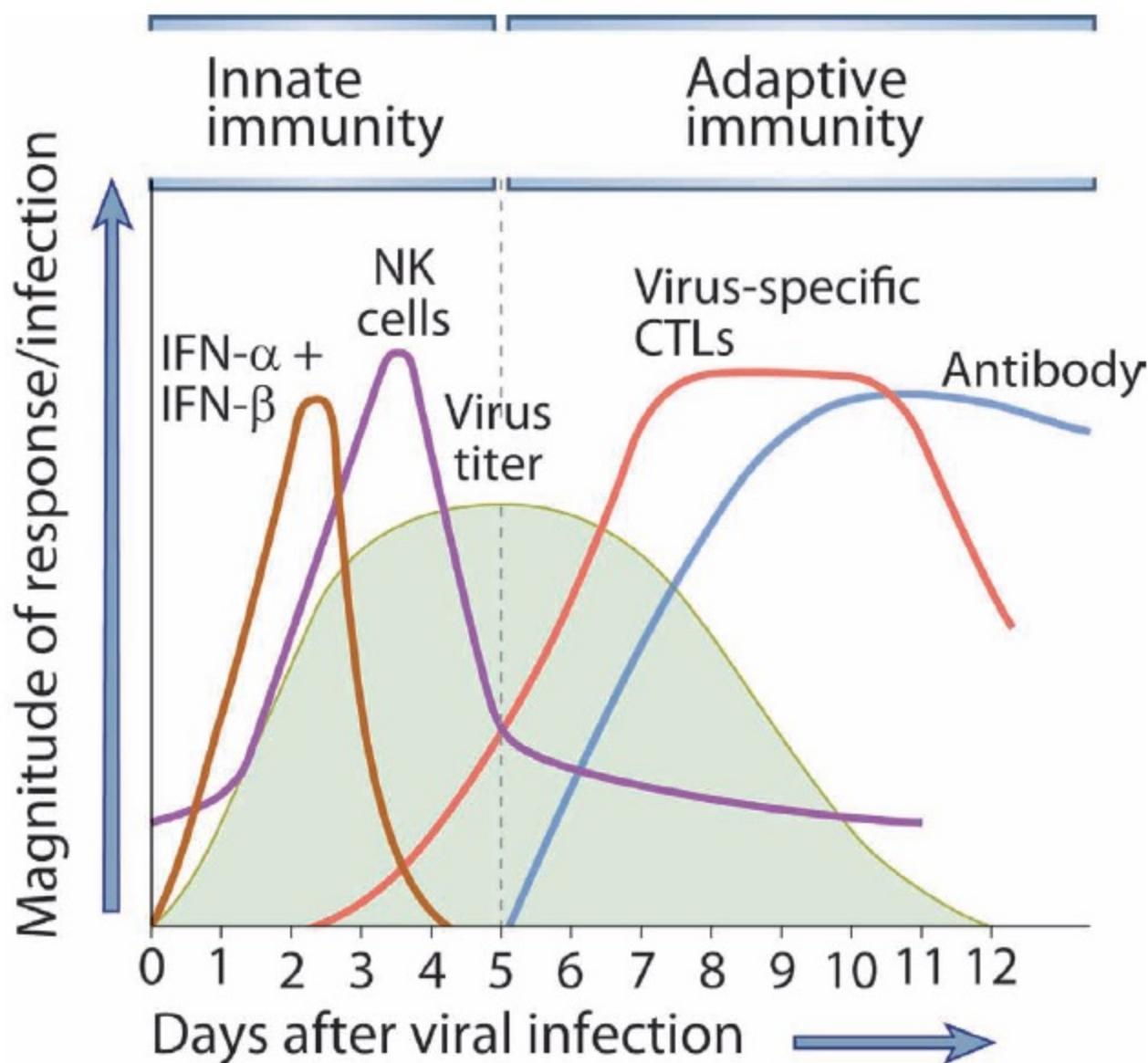


Fig 15-6A

Innate Immunity to Viruses

- inhibition by type I interferons (IFN- α , IFN- β)
 - Type I interferons produced by infected cells, plasmacytoid dendritic cells
 - Type I interferons function to inhibit viral replication in both infected and uninfected cells by inducing an "antiviral state."
- NK cell-mediated killing of infected cells
 - important mechanism early in the course of infection, before adaptive immune responses have developed
 - NK cells also recognize infected cells in which the virus has shut off class I MHC expression as an escape mechanism from CTLs because the absence of class I releases NK cells from a normal state of inhibition

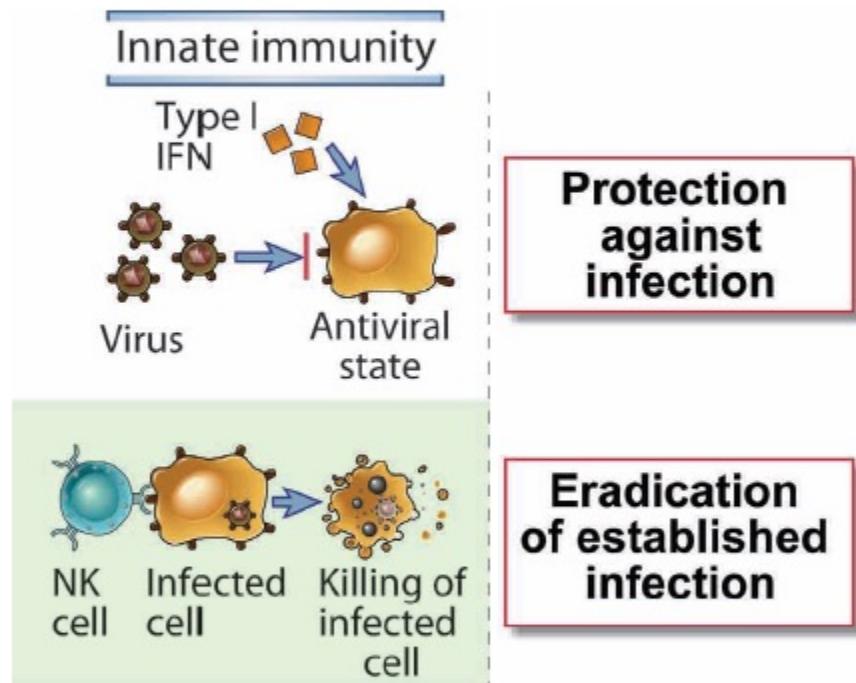


Fig. 15-6B

Induction of Type I Interferons by Viruses

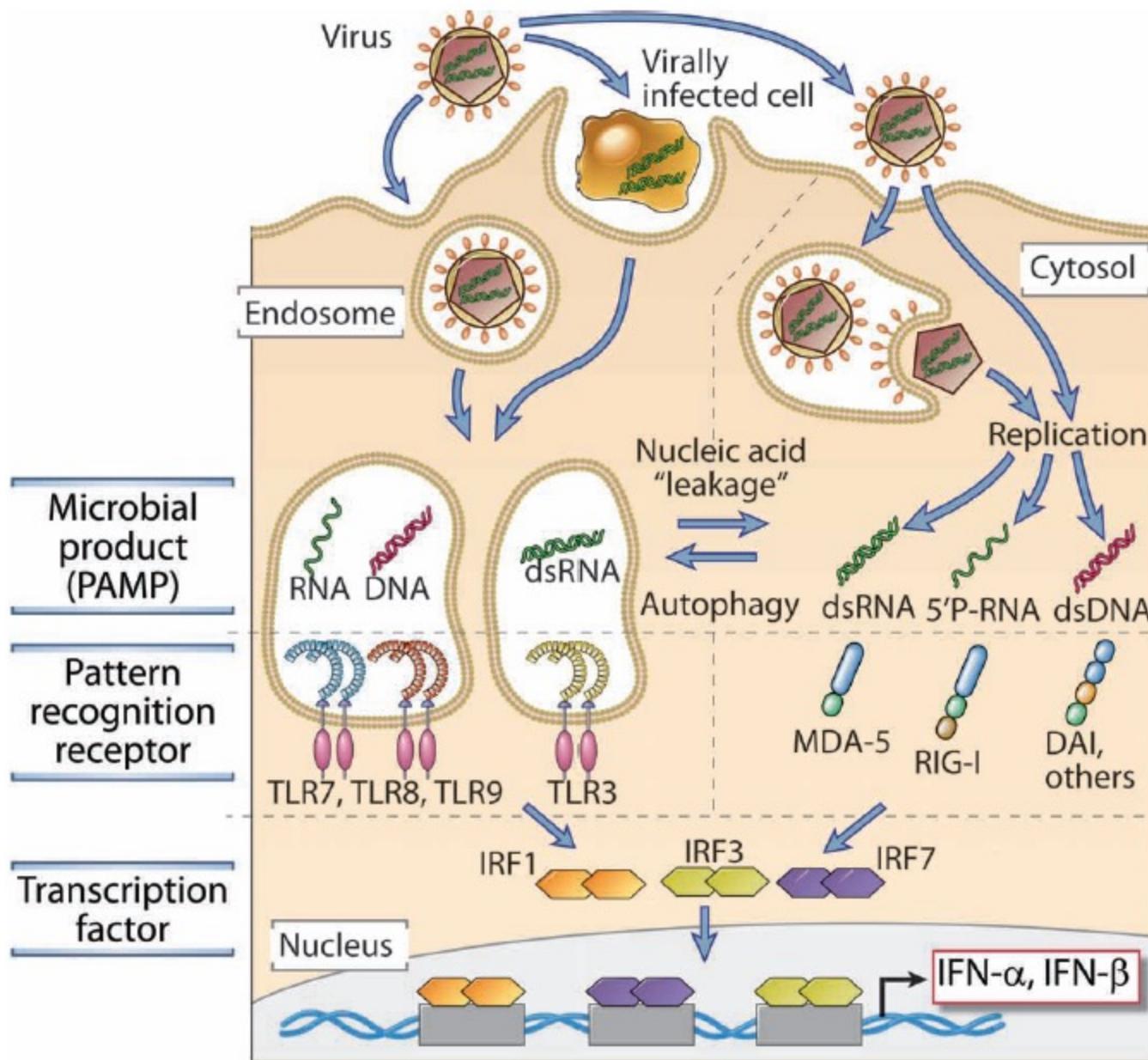


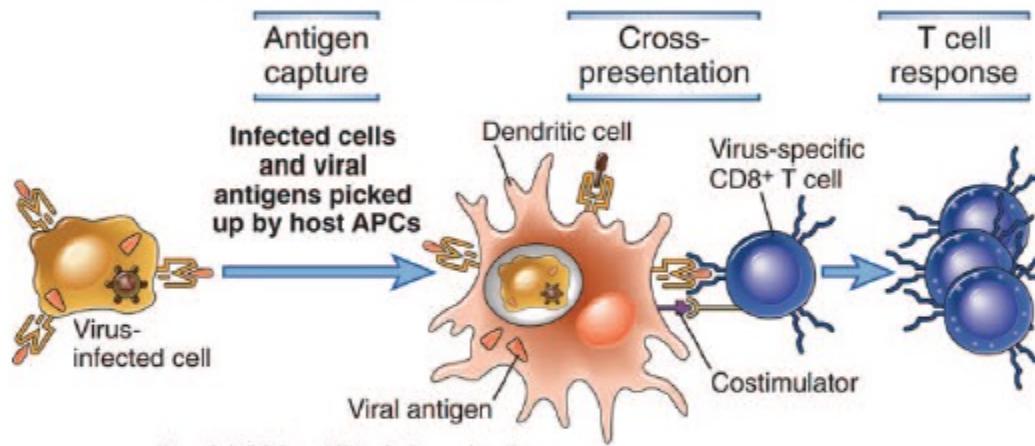
Fig. 15-7

Adaptive Humoral Immunity to Viruses

- Antiviral antibodies
 - high affinity antibodies blocking extracellular virions (early in infection or after budding of virus or cell death)
 - bind to viral envelope or capsid antigens and function mainly as neutralizing antibodies to prevent virus attachment and entry into host cells. IgA isotype are important for neutralizing viruses within the respiratory and intestinal tracts (oral immunization against poliomyelitis works by inducing mucosal immunity).
 - opsonize viral particles and promote their clearance by phagocytes.
 - once the viruses enter cells, they are inaccessible to antibodies.
- Humoral immunity induced by previous infection or vaccination is able to protect individuals from viral infection but cannot by itself eradicate established infection.
- Complement activation may also participate in antibody-mediated viral immunity (phagocytosis and possibly direct lysis of enveloped viruses)
- resistance to a particular virus, induced by either infection or vaccination, is often specific for the serologic (antibody-defined) type of the virus (influenza)

CTL responses to Viruses

- Elimination of viruses that reside within cells is mediated by cytotoxic T lymphocytes CTLs: CD8+ T cells that recognize cytosolic viral peptides presented by class I MHC molecules
- Professional antigen-presenting cells (APC) can phagocytose infected cells and present processed antigens to naive CD8+ T cells (cross-presentation or cross-priming)

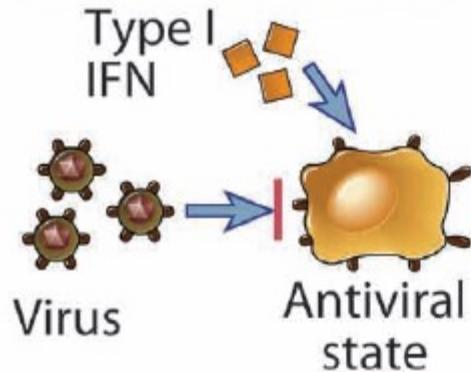


Abbas et al: Cellular and Molecular Immunology, 7e.
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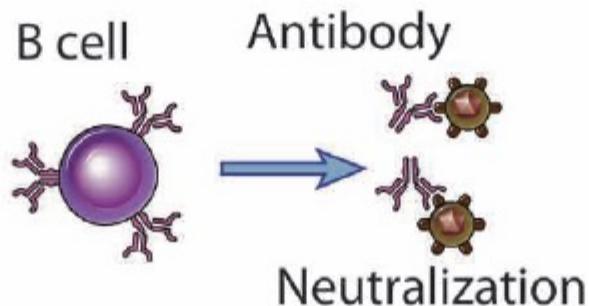
- Full differentiation of CD8+ CTLs often requires cytokines produced by CD4+ helper cells or costimulators expressed on infected cells
- adoptive transfer of virus-specific, class I-restricted CTLs induce protection in T cell deficient individuals
- infected cells may produce some viral proteins that are invariant, so that CTL-mediated defense remains effective against viruses that alter their surface antigens

CTL responses to Viruses

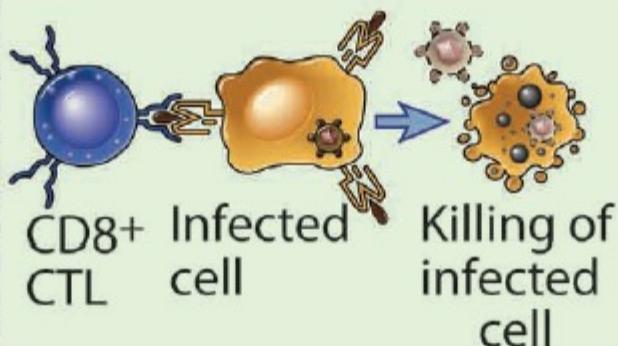
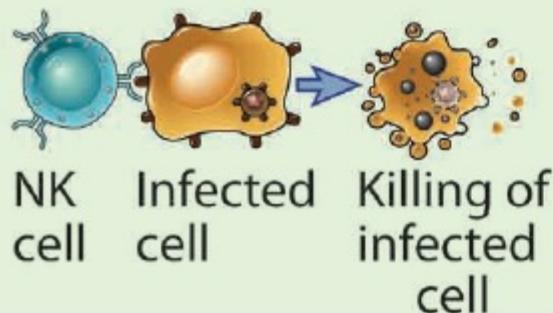
Innate immunity



Adaptive immunity



**Protection
against
infection**



**Eradication
of established
infection**

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Latent viral infections (virus latency)

- Viral DNA persists in host cells but the virus does not replicate or kill infected cells
- State of balance between infection and the immune response
- CTLs are generated in response to the virus that can control the infection but not eradicate it => the virus persists in infected cells => any deficiency in the host immune response => reactivation of the latent infection => cytopathic effects and spread of the virus.
Cytopathic effects may include lysis of infected cells or uncontrolled proliferation of the cells

Tissue injury caused by the adaptive response

- Tissue injury may be caused by CTLs
 - Lymphocytic choriomeningitis virus (LCMV) infection in mice
 - inflammation of the spinal cord meninges.
 - LCMV infects meningeal cells, but noncytopathic, does not injure the infected cells directly
 - virus-specific CTLs kill infected meningeal cells during a physiologic attempt to eradicate the infection
 - Meningitis develops in normal mice with intact immune systems, but T cell-deficient mice do not develop disease and instead become carriers of the virus => immunodeficient individuals are more susceptible to LCMV-induced disease !
 - Hepatitis B virus infection in humans
 - Infected immunodeficient persons do not develop the disease but become carriers who can transmit the infection to otherwise healthy persons
 - Livers of patients with acute and chronic active hepatitis contain large numbers of CD8+ T cells, and hepatitis virus-specific, class I MHC-restricted CTLs can be isolated from liver biopsy specimens and propagated in vitro
- Circulating immune complexes composed of viral antigens and specific antibodies
 - Complexes are deposited in blood vessels and lead to systemic vasculitis
 - Some viral proteins contain amino acid sequences that are also present in some self antigens: "molecular mimicry," => antiviral immunity can lead to immune responses against self antigens

Immune Evasion by Viruses

- Viruses can alter their antigens (point mutations and reassortments) and are thus no longer targets of immune responses (antigenic drift)
examples: influenza virus, rhinovirus, human immunodeficiency virus (HIV)
- Some viruses inhibit class I MHC-associated presentation of cytosolic protein antigens
examples: Herpes simplex virus, cytomegalovirus (CMV)
- Some viruses produce molecules that inhibit the immune response (cytokine or chemokine receptors)
examples: Vaccinia, Poxviruses, CMV, Epstein-Barr virus (EBV)
- Some chronic viral infections are associated with failure of CTL responses, which allows viral persistence
example: lymphocytic choriomeningitis virus
- Viruses may infect and either kill or inactivate immunocompetent cells
example: HIV survives by infecting and eliminating CD4+ T cells

Antigenic drift is a mechanism for variation in viruses by accumulating mutations within genes, which code for antigen-binding sites.

Antigenic shift is a process of combining two types of viruses to form a new subtype with a mixture of surface antigens of the original viruses.

ANTIGENIC DRIFT VERSUS ANTIGENIC SHIFT

ANTIGENIC DRIFT

A mechanism for variation by viruses, which involves the accumulation of mutations within the antigen-binding sites

The variation in the antigenic pool is by the accumulation of gene mutations

A minor antigenic change

Results in a new viral strain

Occurs frequently

The new viral strain may infect the hosts of the same species

Easy to treat

Occurs in Influenza virus A, B, and C

Gives rise to epidemics between pandemics

ANTIGENIC SHIFT

A sudden shift in the antigenicity of a virus resulting from the combination of the genomes of two viral strains

Two different strains of viruses combine to form a new subtype

A major antigenic change

Results in a new subtype of the virus

Occurs once in a time

The new viral subtype may infect another host in a different species

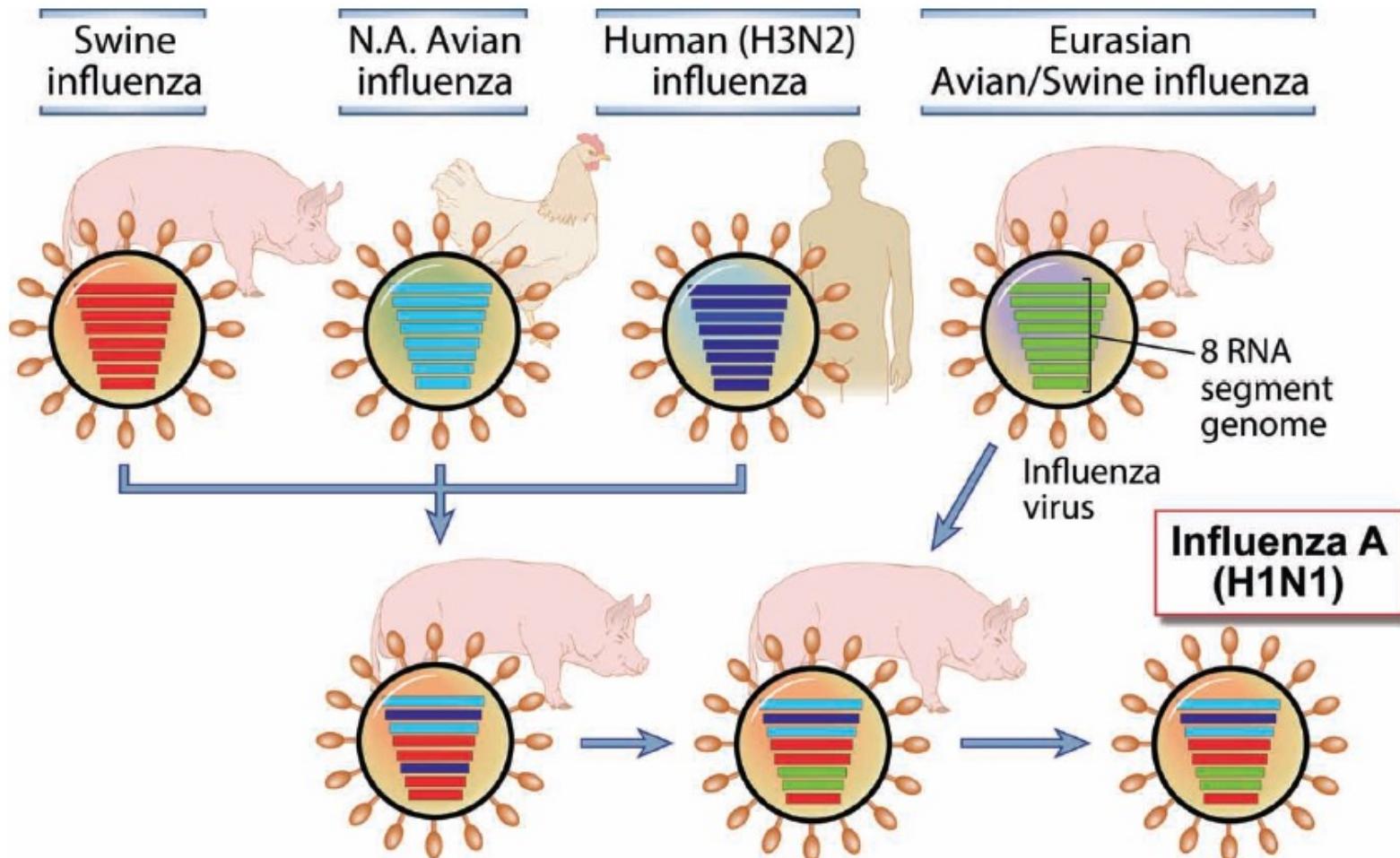
Difficult to treat

Occurs in Influenza virus A

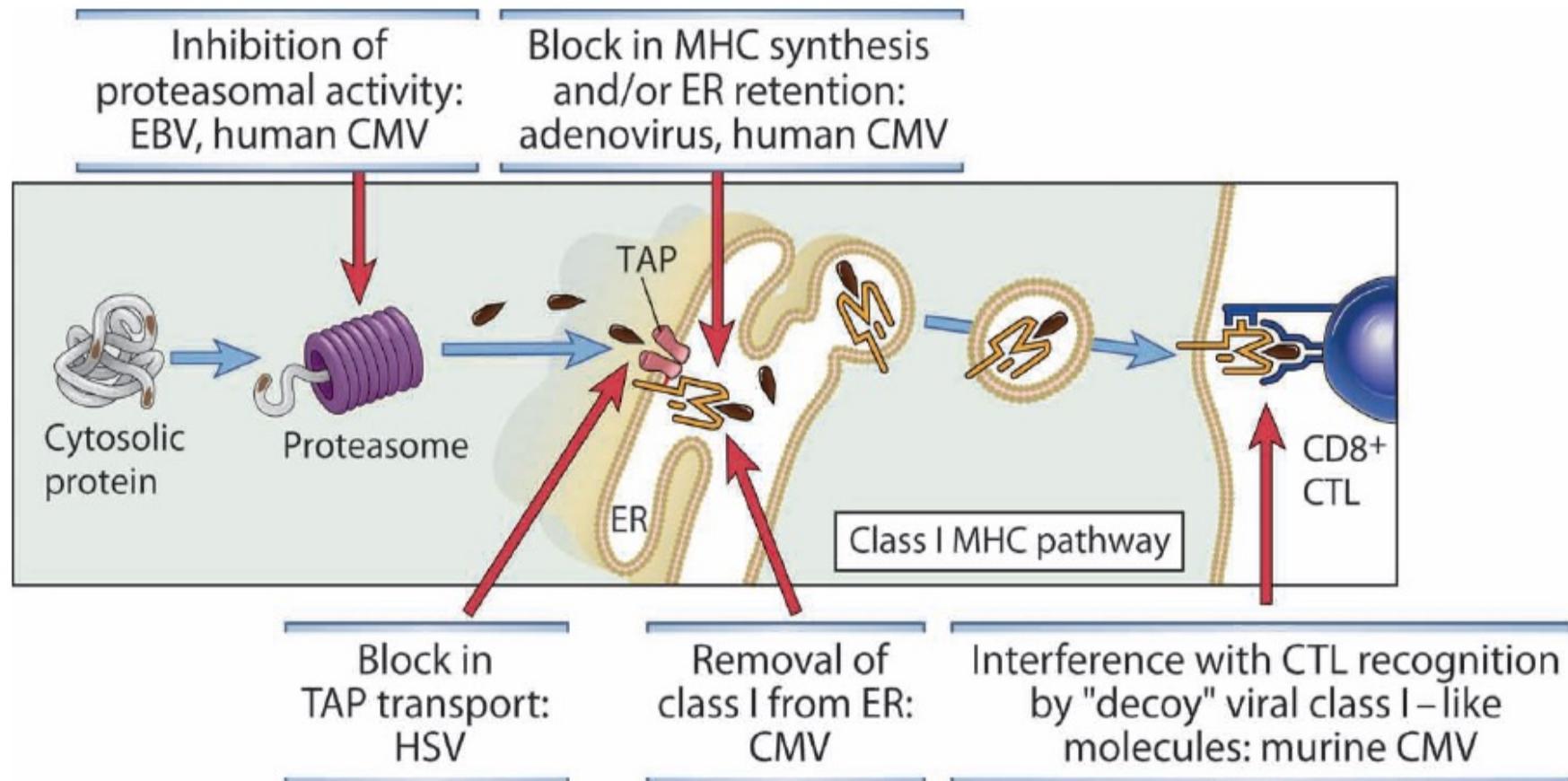
Gives rise to pandemics

Antigenic Shift

Genetic Recombination in Influenza Virus



Viruses Inhibition of Antigen Presentation



EBV: Epstein-Barr virus
CMV: Cyto Megalo virus
HSV: Herpes simplex virus

Fig. 15-9

Immunity to Parasites

Parasite	Human Diseases	Mechanisms of Pathogenicity
Protozoa		
<i>Plasmodium</i> species	Malaria	Antibodies and CD8 ⁺ CTLs
<i>Leishmania donovani</i>	Leishmaniasis (mucocutaneous disseminated)	CD4 ⁺ T _H 1 cells activate macrophages to kill phagocytosed parasites
<i>Trypanosoma brucei</i>	African trypanosomiasis	Antibodies
<i>Entamoeba histolytica</i>	Amebiasis	Antibodies, phagocytosis
Metazoa		
<i>Schistosoma</i> species	Schistosomiasis	Killing by eosinophils, macrophages
Filaria, e.g., <i>Wuchereria bancrofti</i>	Filariasis	Cell-mediated immunity; role of antibodies?

Table 15-4

Immunity to Parasites

- Parasitic infections refer to infection with animal parasites such as protozoa, helminths, and ectoparasites (e.g., ticks and mites)
- About 30% of the world's population suffers from parasitic infestations.
Malaria alone affects more than 100 million people worldwide and is responsible for 1 to 2 million deaths annually.
- Complex life cycles, part of which occurs in humans (or other vertebrates) and part of which occurs in intermediate hosts
 - malaria and trypanosomiasis are transmitted by insect bites
 - schistosomiasis is transmitted by exposure to water in which infected snails reside.
- Most parasitic infections are chronic because of weak innate immunity and the ability of parasites to evade or resist elimination by adaptive immune responses
- Many antiparasite drugs are not effective at killing the organisms => repeated chemotherapy in endemic areas => expense and logistic problems
=> development of prophylactic vaccines for parasites has long been considered an important goal for developing countries.

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Innate Immunity to Parasites

- The principal innate immune response to protozoa is phagocytosis, but resistance to phagocytic killing and replication within macrophages
- Some protozoa express surface molecules that are recognized by TLRs and activate phagocytes
 - Plasmodium species, Toxoplasma gondii, and Cryptosporidium all express glycosyl phosphatidylinositol lipids that can activate TLR2 and TLR4
- Phagocytes may also attack helminthic parasites and secrete microbicidal substances to kill organisms that are too large to be phagocytosed. However, many helminths have thick teguments that make them resistant to the cytotoxic mechanisms of neutrophils and macrophages, and they are too large to be ingested by phagocytes
- Some helminths may activate the alternative pathway of complement, some parasites have developed resistance to complement-mediated lysis

Adaptive Immunity to Parasites

- Different parasites elicit distinct adaptive immune responses
 - Some pathogenic protozoa have evolved to survive within host cells, so protective immunity against these organisms is mediated by mechanisms similar to those that eliminate intracellular bacteria and viruses.
 - Metazoa (helminths) survive in extracellular tissues => their elimination is often dependent on special types of antibody responses
- The principal defense mechanism against protozoa that survive within macrophages is cell-mediated immunity, particularly macrophage activation by T_{H1} cell-derived cytokines.
 - Leishmania major in mice: dominance of T_{H1} or T_{H2} responses determines disease resistance or susceptibility
- Protozoa that replicate inside various host cells and lyse these cells stimulate specific antibody and CTL responses, similar to cytopathic viruses
 - malaria parasite resides mainly in red blood cells and in hepatocytes during its life cycle: CTL response against parasites residing in hepatocytes is an important defense against the spread of this intracellular protozoan.
- The cytokine IFN- γ has been shown to be protective in many protozoal infections, including malaria, toxoplasmosis, and cryptosporidiosis
- Defense against many helminthic infections is mediated by the activation of T_{H2} cells, which results in production of IgE antibodies and activation of eosinophils and mast cells => expulsion and destruction of the parasites.

Immune Evasion by Parasites

- Parasites change their surface antigens during their life cycle in vertebrate hosts. Two forms of antigenic variation are well defined:
 - stage-specific change in antigen expression, such that the mature tissue stages of parasites produce antigens different from those of the infective stages
 - continuous variation of major surface antigens seen in African trypanosomes (*T. brucei* and *T. rhodesiense*: programmed variation in expression of the genes encoding the major surface antigen (hundred waves of parasitemia can occur in an infection)
- Parasites become resistant to immune effector mechanisms during their residence in vertebrate hosts
 - schistosome larvae, which travel to the lungs of infected animals and during this migration develop a tegument that is resistant to damage by complement and by CTLs
- Protozoan parasites may conceal themselves from the immune system
 - Some helminthic parasites reside in intestinal lumens and are sheltered from cell-mediated immune effector mechanisms.
 - *Entamoeba histolytica* is a protozoan parasite that sheds antigens and can also convert to a cyst form in the lumen of the large intestine.
- Inhibition of host immune responses
 - T cell anergy to parasite antigens (schistosomiasis, filarial infections). mechanism?
 - *Leishmania* stimulate the development of regulatory T cells
 - More nonspecific and generalized immunosuppression is observed in malaria and African trypanosomiasis (production of immunosuppressive cytokines)

Strategies for Vaccine Development

The first vaccine

The birth of immunology as a science dates from Edward Jenner's successful vaccination against smallpox in 1796.

The word vaccine was coined by Jenner and comes from the Latin "vacca" for cows.



Edward Jenner (1749 - 1823)

Basics of vaccinology

- The fundamental principle of vaccination is to administer a killed or attenuated form of an infectious agent, or a component of a microbe, that does not cause disease but elicits an immune response that provides protection against infection by the live, pathogenic microbe.
- The success of vaccination in eradicating infectious disease is dependent on several properties of the microbes:
 - no latency
 - little or no antigenic variation
 - no interference with the host immune response
 - infections limited to human hosts (no animal reservoirs)
- Most vaccines work by inducing humoral immunity: prevent infection
- Best vaccines:
 - stimulate the development of long-lived plasma cells
 - produce high-affinity antibodies
 - generate memory B cells.
 - These aspects of humoral immune responses are best induced by the germinal center reaction, which requires help by protein antigen-specific CD4+ T cells.

Types of Vaccines (Active immunization)

- Attenuated or inactivated bacterial and viral vaccines
- Purified antigen (subunit) vaccine
- Synthetic antigen vaccine
- DNA vaccines

Attenuated and Inactivation Bacterial and Viral Vaccines

- **Attenuated vaccines** composed of live nonpathogenic microbes but can no longer cause disease: microbe virulence is attenuated.
Great advantage: elicit all the innate and adaptive immune responses (both humoral and cell mediated) that the pathogenic microbe would, => ideal way of inducing protective immunity.
- **Inactivated vaccines** composed of dead microbes while retaining immunogenicity
- Live, attenuated bacteria were first shown by Louis Pasteur to confer specific immunity. The attenuated or killed bacterial vaccines in use today generally induce limited protection and are effective for only short periods.
- Live, attenuated viral vaccines are usually more effective; polio, measles, and yellow fever are three good examples.
Long-lasting specific immunity.
- Some attenuated viral vaccines (e.g., polio) may cause disease in immune-compromised hosts, and for this reason inactivated poliovirus vaccines are no more commonly used.
- Major concern with attenuated viral or bacterial vaccines: safety.
- A widely used inactivated vaccine of considerable public health importance is the influenza vaccine. A second type of influenza vaccine is made up of live attenuated viruses and is used as a nasal spray.

Purified Antigen (Subunit) Vaccines

- Composed of antigens purified from microbes or inactivated toxins
- Usually administered with an adjuvant
- Prevention of diseases caused by bacterial toxins: harmless but immunogenic "toxoids" => induce strong antibody responses (diphtheria and tetanus)
- Bacterial polysaccharide antigens pneumococcus and H. influenzae. polysaccharides are T-independent antigens -> elicit low-affinity antibody responses and may be poorly immunogenic in infants => conjugate vaccines: coupling the polysaccharides to proteins (hapten-carrier) => high-affinity antibody responses (H. influenzae, pneumococcal, and meningococcal vaccines are conjugate vaccines)
- Purified protein vaccines stimulate helper T cells and antibody responses, but they do not generate potent CTLs.
Exogenous proteins are inefficient at entering the class I MHC pathway of antigen presentation and cannot readily displace peptides from surface class I molecules

Synthetic Antigen Vaccines

- Identify the most immunogenic microbial antigens or epitopes
=> synthesize in the lab and use the synthetic antigens as vaccines
- It is possible to deduce the protein sequences of microbial antigens from nucleotide sequence data and to prepare large quantities of proteins by recombinant DNA technology
- Vaccines made of recombinant DNA-derived antigens are now in use for hepatitis virus, herpes simplex virus, foot-and-mouth disease virus (a major pathogen for livestock), human papillomavirus, and rotavirus
- In the most widely used human papillomavirus vaccine, recombinant viral proteins from four viral strains (HPV 6, 11, 16, and 18) are made in yeast and combined with an adjuvant.
 - HPV 6 and 11 are common causes of warts
 - HPV 16 and 18 are the most common HPV strains linked to cervical cancer. This antiviral vaccine is therefore also a preventive cancer vaccine.

DNA Vaccines

- Developed on the basis of an unexpected observation: Inoculation of a plasmid containing complementary DNA (cDNA) encoding a protein antigen leads to strong and long-lived humoral and cell-mediated immune responses to the antigen. It is likely that APCs, such as dendritic cells, are transfected by the plasmid and the cDNA is transcribed and translated into immunogenic protein that elicits specific responses.
- Unique feature of DNA vaccines: provide the only approach, other than live viruses, for eliciting strong CTL responses because the DNA-encoded proteins are synthesized in the cytosol of transfected cells.
- Bacterial plasmids are rich in unmethylated CpG nucleotides and are recognized by TLR9
Cytosine phosphate guanine = CpG
 - => innate immune response that enhances adaptive immunity
 - => plasmid DNA vaccines could be effective even when administered without adjuvants
- Easy to manipulate cDNAs, no refrigeration required in the field, and ability to coexpress other proteins that may enhance immune responses (such as cytokines and costimulators)
- Not as effective as hoped in clinical trials, and the factors that determine the efficacy of these vaccines, especially in humans, are still not fully defined.

Adjuvants and Immunomodulators

- The initiation of T cell-dependent immune responses against protein antigens requires that the antigens be administered with adjuvants. Most adjuvants elicit innate immune responses, with increased expression of costimulators and production of cytokines such as IL-12 that stimulate T cell growth and differentiation.
- Heat-killed bacteria are powerful adjuvants: OK in experimental animals
BUT severe local inflammation: not for use in humans
- Development of safe and effective adjuvants for use in humans
 - aluminum hydroxide gel (to promote B cell responses)
 - lipid formulations (ingested by phagocytes)
- Alternative to adjuvants: natural substances that stimulate T cell responses together with antigens.
 - IL-12 incorporated in vaccines promotes strong cell-mediated immunity.
 - Plasmid DNA has intrinsic adjuvant-like activities, and it is possible to incorporate costimulators (e.g., B7 molecules) or cytokines into plasmid DNA vaccines

Passive Immunization

- Passive immunization: transfer of specific antibodies
- Lifesaving: Most commonly used for rapid treatment of potentially fatal diseases
 - toxins, such as tetanus
 - rabies and hepatitis
 - snake venom
- Short-lived:
 - no host response to the immunization
 - protection lasts only as long as the injected antibody persists
 - does not induce memory (no protection against subsequent exposure)