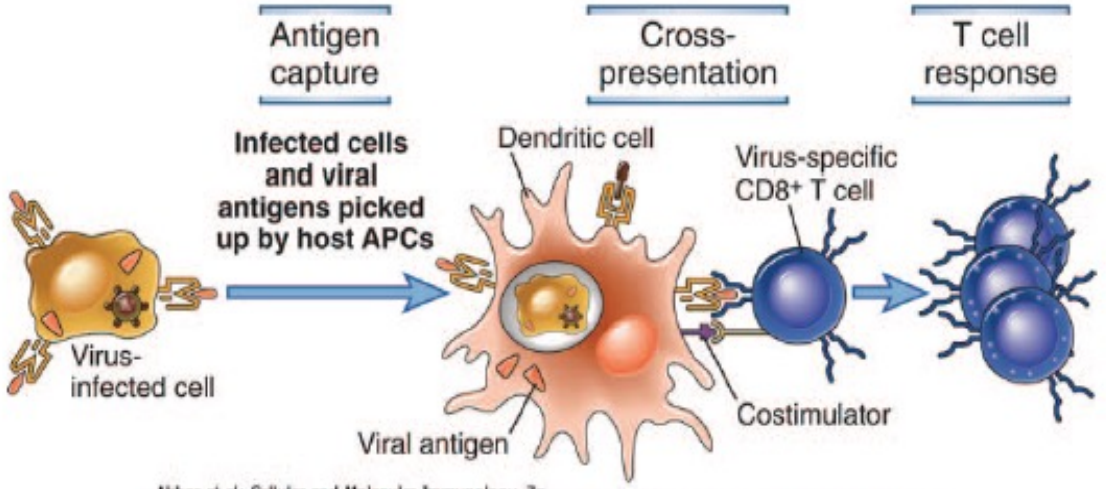
4 Nov, BT 304
Lecture 35

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)

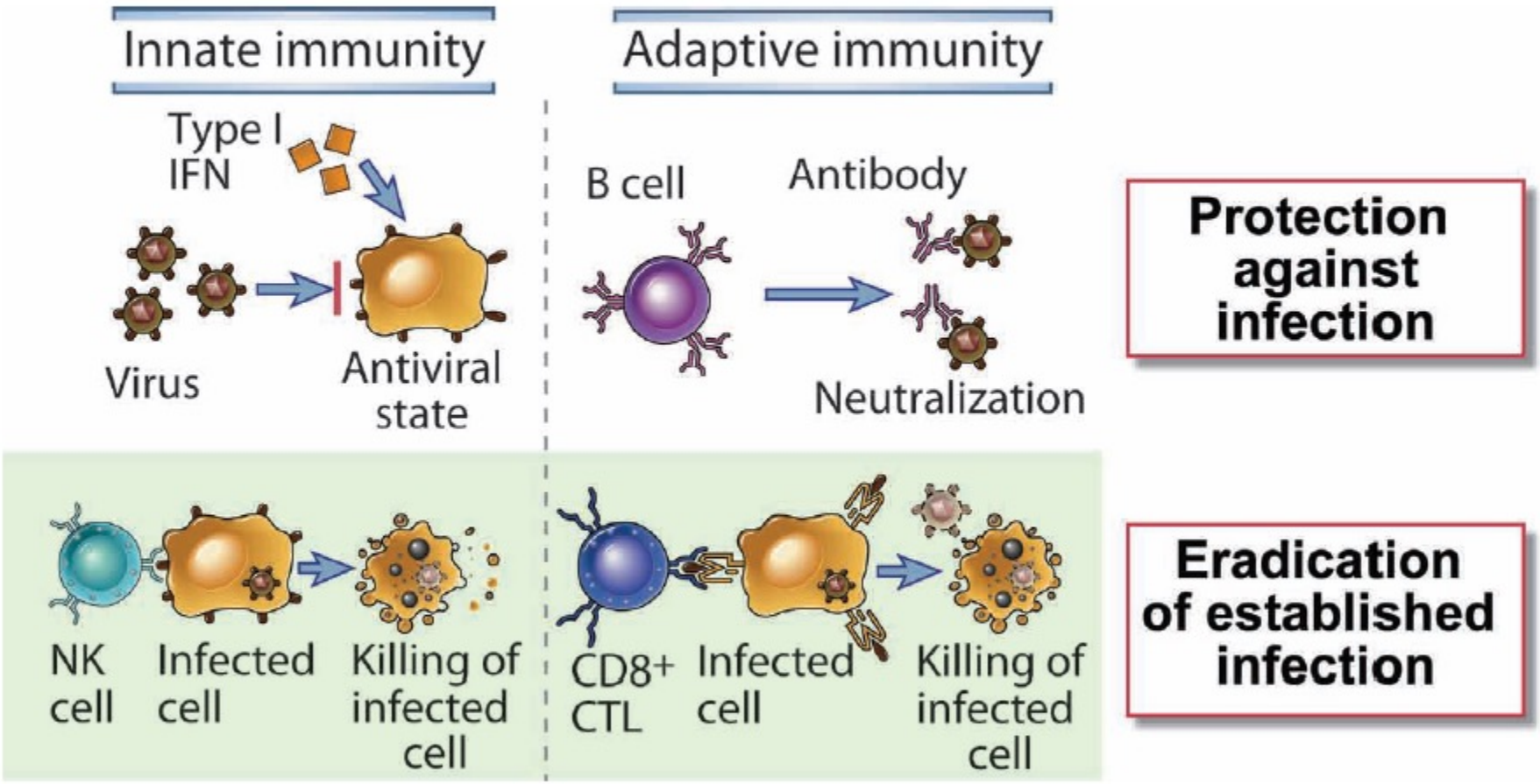
CTL responses to Viruses

- 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)



- 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



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 imunodeficiency 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, Eipstein-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

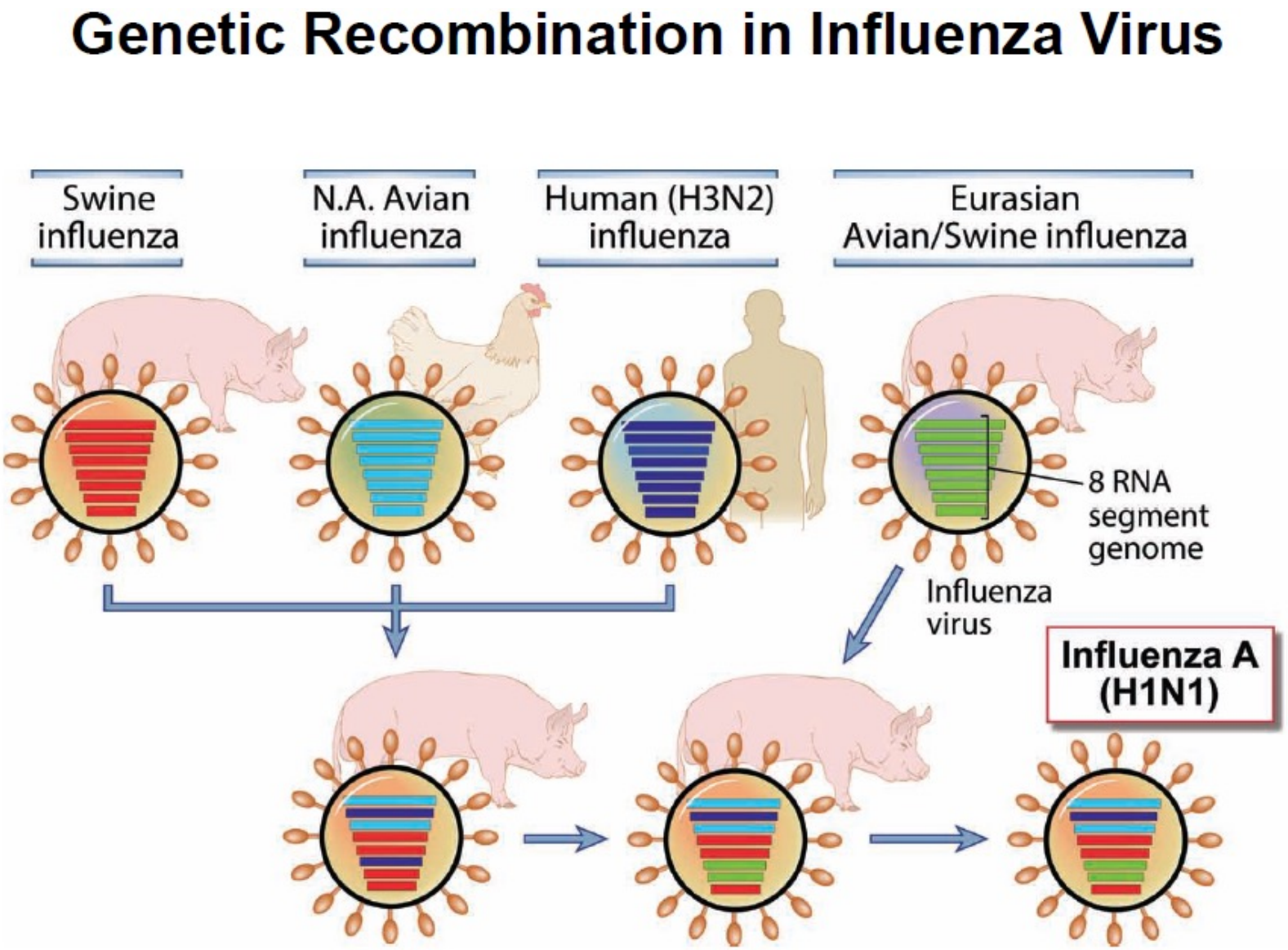
Antigenic drift is a mechanism for variation in viruses by accumulating mutations within genes, which code for antigen-binding sites.

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.

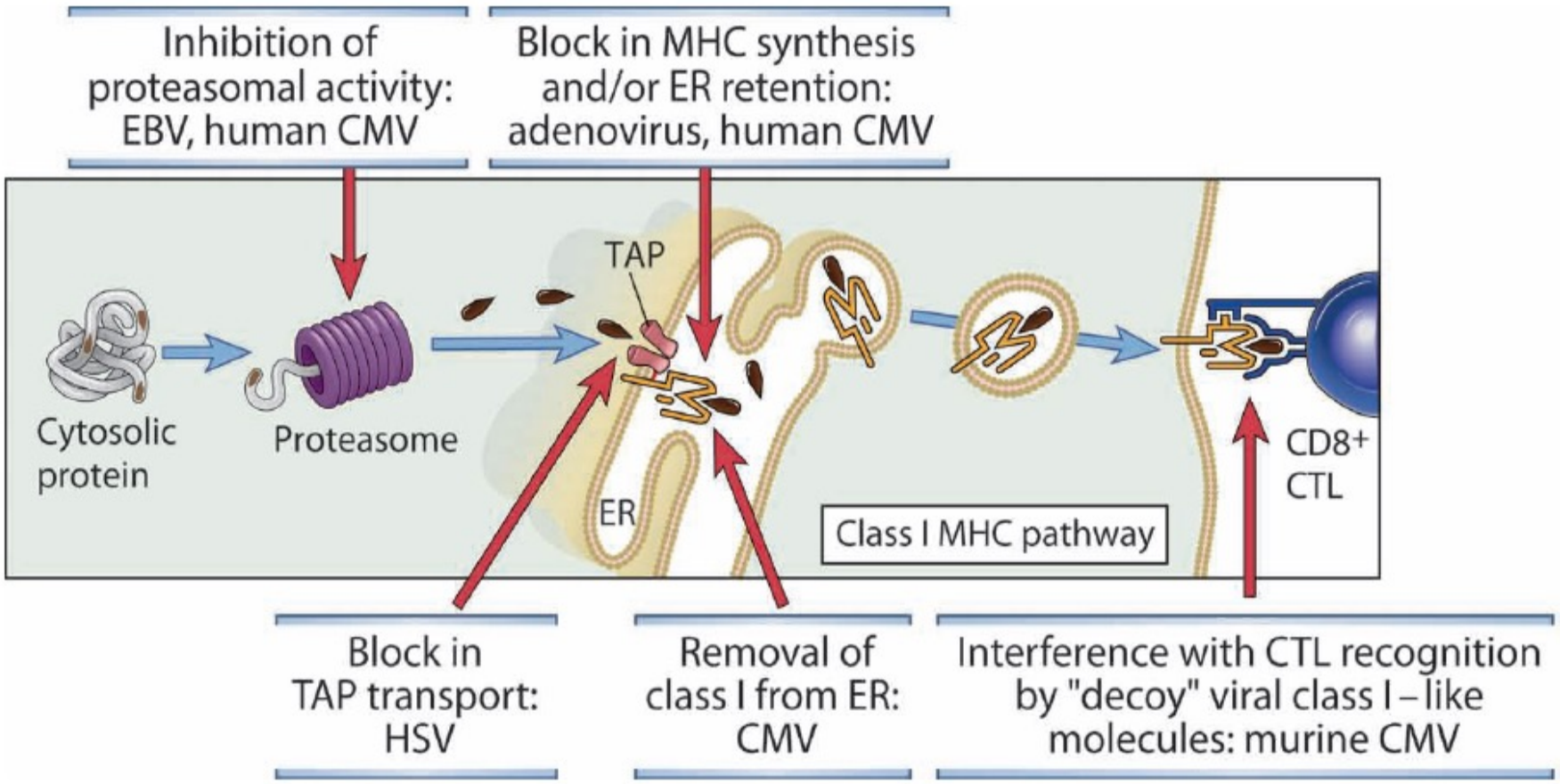
ANTIGENIC DRIFT VERSUS ANTIGENIC SHIFT

ANTIGENIC DRIFT	ANTIGENIC SHIFT
A mechanism for variation by viruses, which involves the accumulation of mutations within the antigen-binding sites	A sudden shift in the antigenicity of a virus resulting from the combination of the genomes of two viral strains
The variation in the antigenic pool is by the accumulation of gene mutations	Two different strains of viruses combine to form a new subtype
A minor antigenic change	A major antigenic change
Results in a new viral strain	Results in a new subtype of the virus
Occurs frequently	Occurs once in a time
The new viral strain may infect the hosts of the same species	The new viral subtype may infect another host in a different species
Easy to treat	Difficult to treat
Occurs in Influenza virus A, B, and C	Occurs in Influenza virus A
Gives rise to epidemics between pandemics	Gives rise to pandemics

Antigenic Shift



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		
Plasmodium species	Malaria	Antibodies and $CD8^+$ CTLs
Leishmania donovani	Leishmaniasis (mucocutaneous disseminated)	$CD4^+$ T_H1 cells activate macrophages to kill phagocytosed parasites
Trypanosoma brucei	African trypanosomiasis	Antibodies
Entamoeba histolytica	Amebiasis	Antibodies, phagocytosis
Metazoa		
Schistosoma species	Schistosomiasis	Killing by eosinophils, macrophages
Filaria, e.g., *Wuchereria bancrofti*	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.

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 cytocidal 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)