Immune Responses to Infectious Disease

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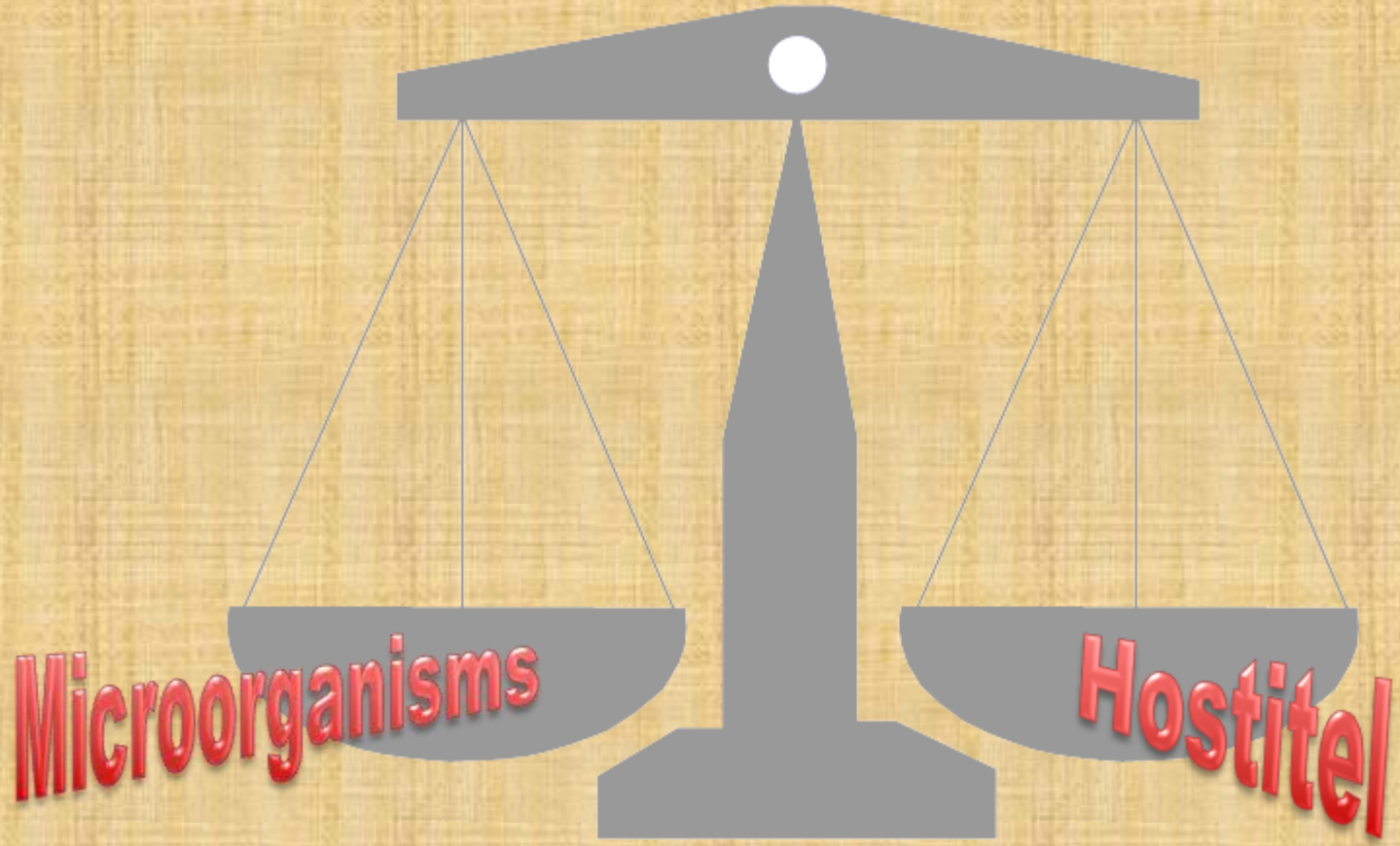
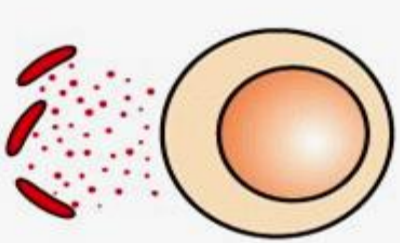
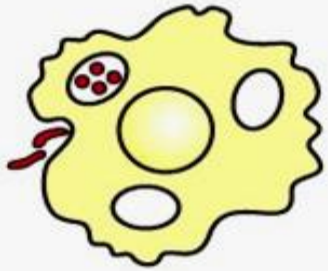
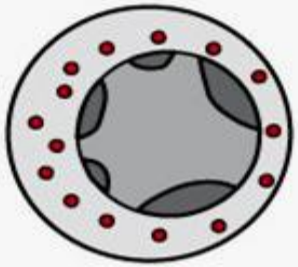
Host-pathogen interaction

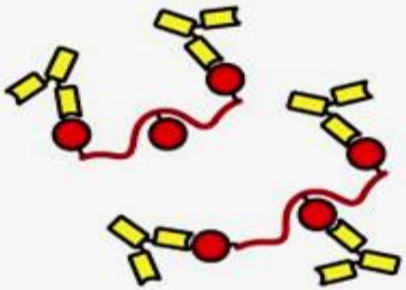
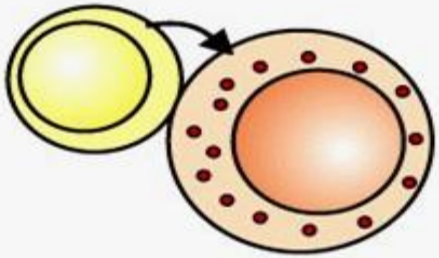


- Mechanisms of pathogenicity
- Immune escape mechanisms
- Number of pathogens
- Genes regulating immune responses
- Health condition of the host

Mechanisms of Pathogen-induced tissue Damage

	Direct mechanisms of tissue damage by pathogens		
	Exotoxin production	**Endotoxin**	**Direct cytopathic effect**
Pathogenic mechanism			
Infectious agent	*Streptococcus pyogenes* *Staphylococcus aureus* *Corynebacterium diphtheriae* *Clostridiumtetani* *Vibrio cholerae*	*Escherichiacoli* *Haemophilus influenzae* *Salmonella typhi* *Shigella* *Pseudomonas aeruginosa* *Yersinia pestis*	Variola Varicella-zoster Hepatitis B virus Polio virus Measles virus Influenza virus Herpes simplex virus Human herpes virus 8 (HHV8)

Mechanisms of Pathogen-induced tissue Damage (continued)

	Indirect mechanisms of tissue damage by pathogens		
	Immune complexes	Anti-host antibody	Cell-mediated immunity
Pathogenic mechanism			
Infectious agent	Hepatitis B virus Malaria *Streptococcus pyogenes* *Treponema pallidum* Most acute infections	*Streptococcus pyogenes* *Mycoplasma pneumoniae*	*Mycobacterium tuberculosis* *Mycobacterium leprae* Lymphocytic choriomeningitis virus *Borrelia burgdorferi* *Schistosoma mansoni* Herpes simplex virus

Bacterial Infections

- 4 steps:
  - Attachment to host cells
  - Proliferation
  - Invasion of host tissue
  - Toxin-induced damage to host cells
- Host defenses act against each of these steps, some bacteria have developed ways to avoid host defences.

Bacterial Infections

- Immunity mainly achieved by antibodies
  - Unless bacteria is capable of intracellular growth
- Depending on # of organisms entering and virulence, different levels of host defense enlisted
  - If inoculum size and virulence is low, phagocytes may be able to eliminate the bacteria

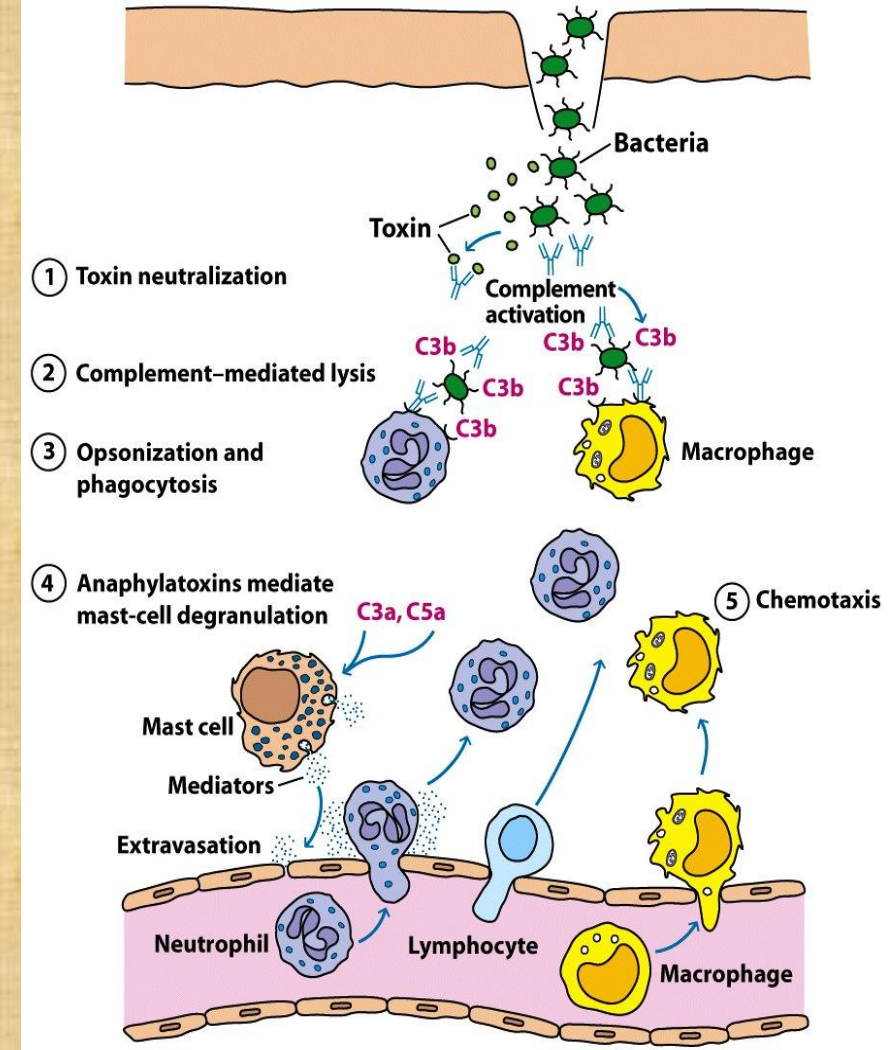


Figure 18-8
Kuby IMMUNOLOGY, Sixth Edition

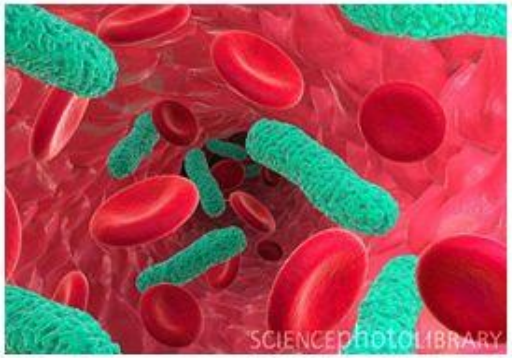
TABLE 18-3 Host immune responses to bacteri

Infection process	Host defense
Attachment to host cells	Blockage of attachment by secretory IgA antibodies
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)
	Complement-mediated lysis and localized inflammatory response
Invasion of host tissues	Ab-mediated agglutination
Toxin-induced damage to host cells	Neutralization of toxin by antibody

Immune responses can contribute to bacterial pathogenesis

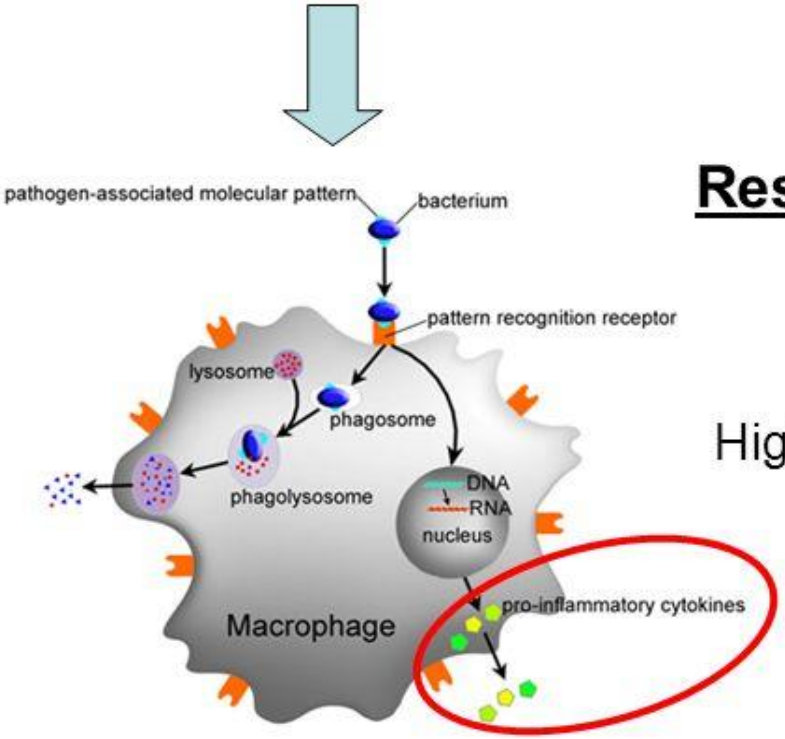
- Overproduction of cytokines
  - Septic shock and toxic shock
- Intracellular bacteria
  - Chronic antigenic activation of CD4+ T cells
  - Leads to tissue destruction
  - Characteristics of delayed-type hypersensitivity
  - Leads to development of granuloma and necrosis

SEPTIC SHOCK



Triggering factors :

- systemic infection (bacteraemia)
- microbial cell wall products and/or toxins released from the pathogens



Result:

Systemic activation of neutrophils and macrophages

↓

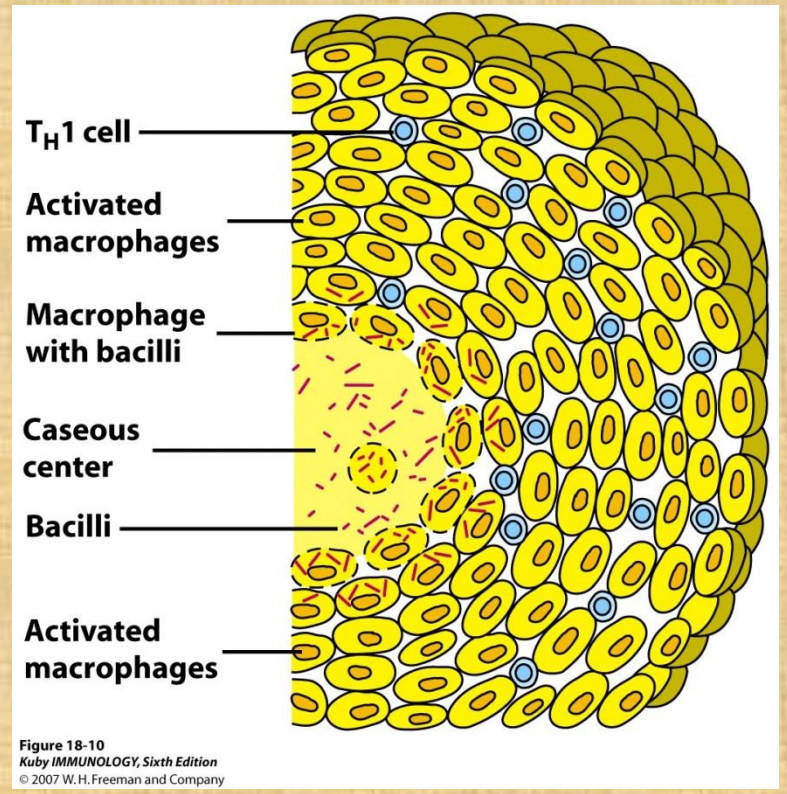
High level of **cytokine** (TNF-alpha) production: „cytokine storm"

↓

Excessive inflammatory response

Tuberculosis

- Intracellular bacillus
- CD4+ T cell response
  - Responsible for most of the tissue damage
  - This necrosis can be seen when tested for TB
  - Sensitized T cell and activated macrophages is the key factor in immunity.



- Tubercle formed in pulmonary tuberculosis

Defence against extracellular bacteria

➢ **Bacteria producing toxins (*C.tetani*, *C.botulinum*, *C.diphtheriae*)**

- Opsonization - complement, lectin or antibodies
- Neutralization - antibodies
- Phagocytosis – neutrophils, macrophages
- B lymphocytes activation and antibodies secretion (IgM, IgA, IgG1)
- Antibodies directed against specific polysaccharides of endotoxins can be protective both by enhancing phagocytosis directly and by fixing complement for lysis.
- Antigenic difference in the polysaccharide component of endotoxins among strains of bacteria cause that the infection with one strain dos not generate protective immunity to re infection with different strain of same species.

• IgMand IgG antibodies directed against the lipid, IgM is more potent neutralizing antibody than IgG

• **Antibody to toxin can neutralize the toxin by several mechanism including:**

- Enhancing clearance by macrophages.

- Blocking binding sites of toxin for its cellular receptor.

❖ *Clostredium tetani*

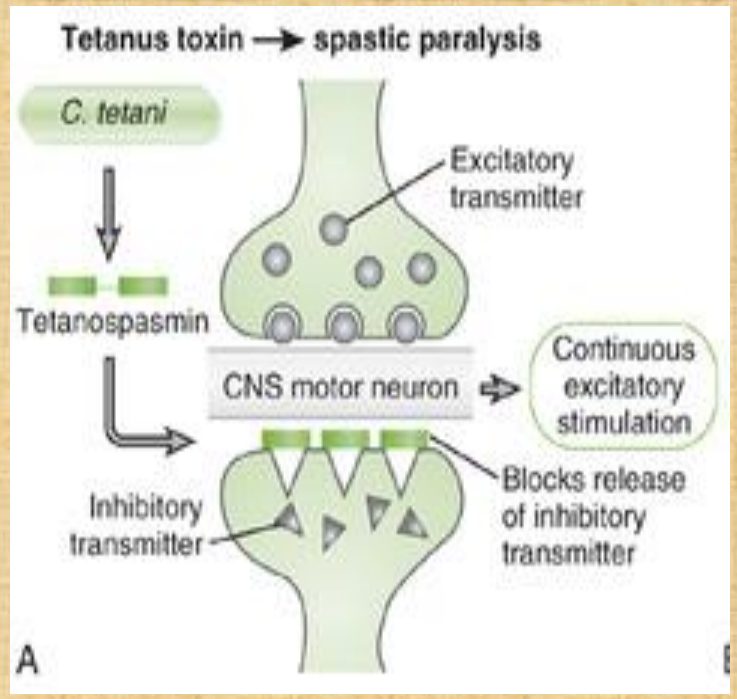
cause tetanus produce neurotoxin called (tetanospasmin) bind to specific glycolipids in nerve cells in peripheral nervous system

• A vaccin prepared from inactivated

• toxin called toxoid prevent disease by

• generating antibodies that neutralize

• the toxin.



❖ *C.botulinum*

Cause food –borne disease occurring when spores or toxin are ingested from contaminated food.

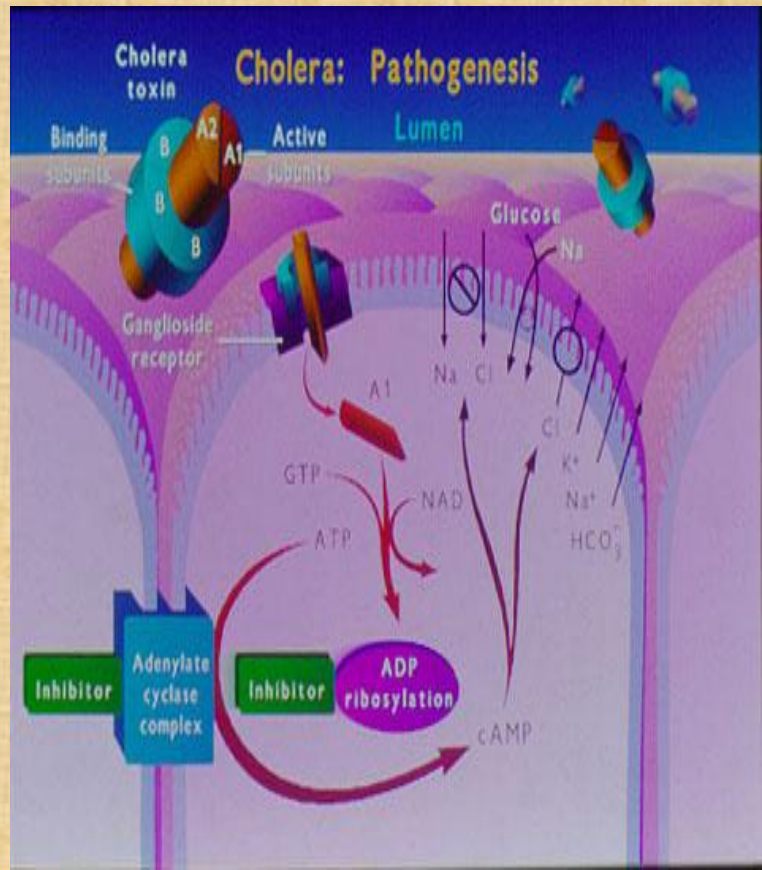
• Botulism is treated with antitoxin.

❖ *Vibrio cholerae*

• Release enterotoxin, antibody to the toxin dos not prevent disease,

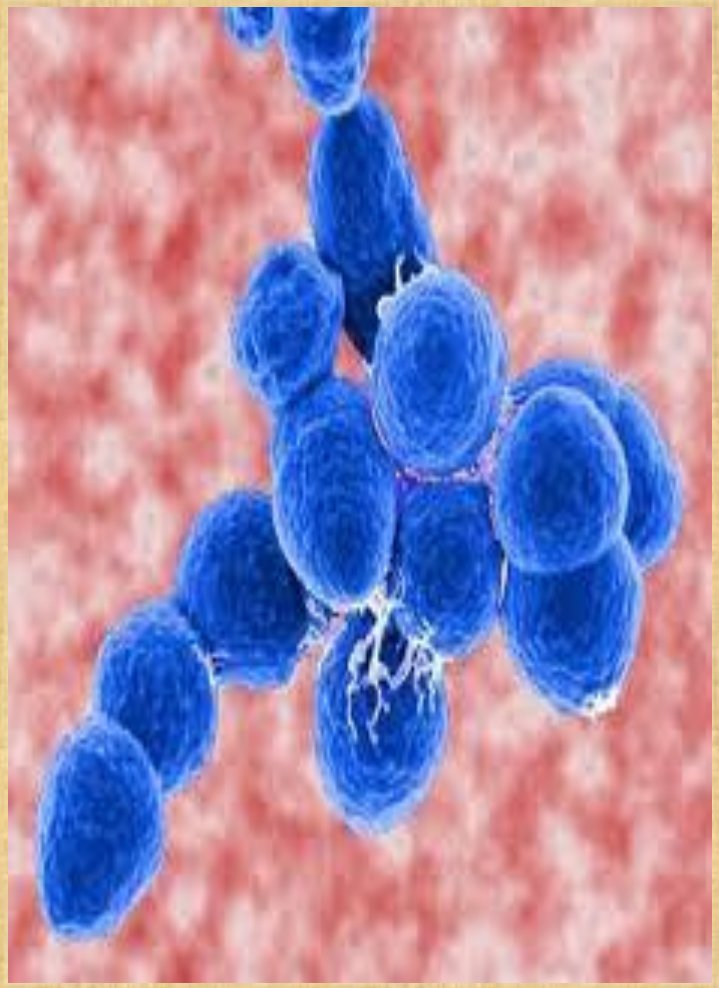
• infection with this bacteria induce systemic and mucosal antibody, mucosal IgA prevents attachment of the bacteria in the gut.

• Cholera vaccines induce IgM and IgG , neither IgM nor IgG function well in the intestienal lumen



➢ bacteria with Polysaccharide capsule (Streptococci, *Neisseria*, *Staphylococci*)

- Capsular polysaccharide inhibits phagocytosis by both macrophages and polymorphnuclear leucocytes
- Opsonization of encapsulated bacteria with antibody and complement is necessary for phagocytes to ingest and kill the pathogens.
- Bacterial vaccines hold great promise for enhancing immunity against encapsulated bacteria



Streptococcus pneumoniae

Streptococcus pyogenes

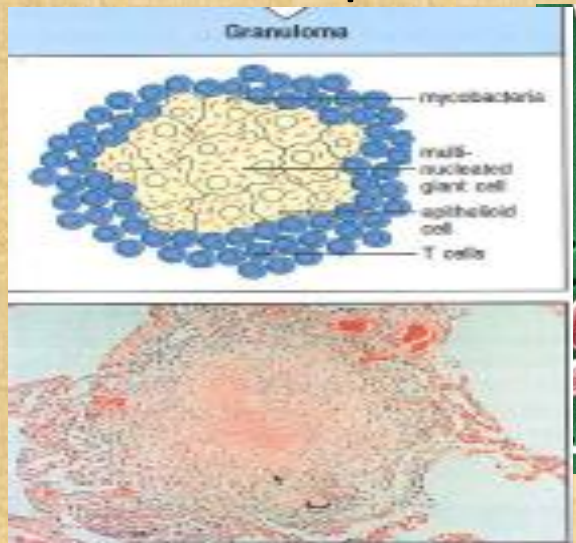
- primary pathogenic, human is a carrier
- toxin production → neutralization
- M protein – resistance to phagocytosis → opsonization
- autoimmune-mediated complications:

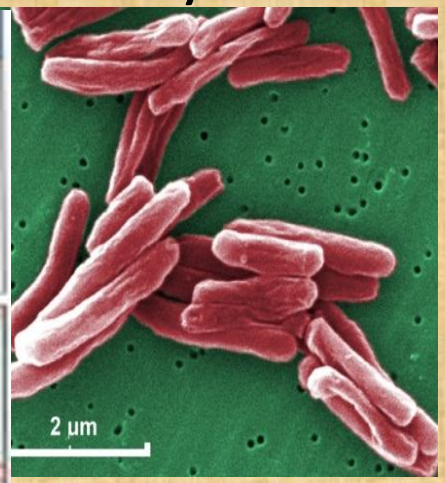
cross-reactivity of antibodies against M protein with host proteins result in rheumatic fever and glumerulonephritis.

Defence against intracellular bacteria

- Intracellular bacteria e.g *Listeria, Mycobacterium, Brucella*
- Antibodies are inefficient
- Phagocytosis – macrophages (IFN-γ production to activate macrophages)
- Th1 response and Th17 response
- (IL-17 production for neutrophils recruitment)
- Cytotoxic T lymphocytes (*Listeria monocytogenes*)
- People with defects of innate and adaptive immunity at risk

• Sensitized T lymphocytes and activated macrophages is the key factor in immunity against intracellular bacteria



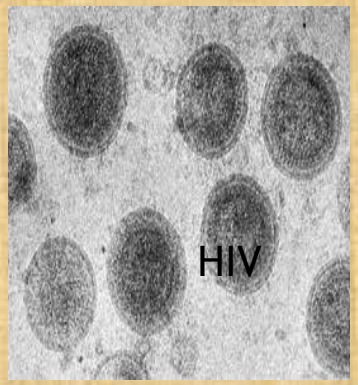


M. tuberculosis

Defence against viruses

- Obligatory intracellular parasites
- Interferons α and β
- Neutralizing antibodies
- Complement activation (virolysis)
- Activity of NK cells attack virus infected cells which express class I MHC.
- Th1 response
- Cytotoxic T lymphocytes (CTL) attack virus infected cell.
- People with T cell immunodeficiency, combined immunodeficiencies and defect in NK cell function (herpesviruses) at risk

Influenza virus



Influenza – "Flu"

- Cause respiratory illness
- Responsible for some of the worse pandemics in history
- Spherical virion surrounded by lipid bilayer acquired from host
  - 2 glycoproteins – hemagglutin (HA) and neuraminidase (NA)
  - Antigenic variation in these (mutations leading to new strains) cause problems in developing sustained immunity in the population

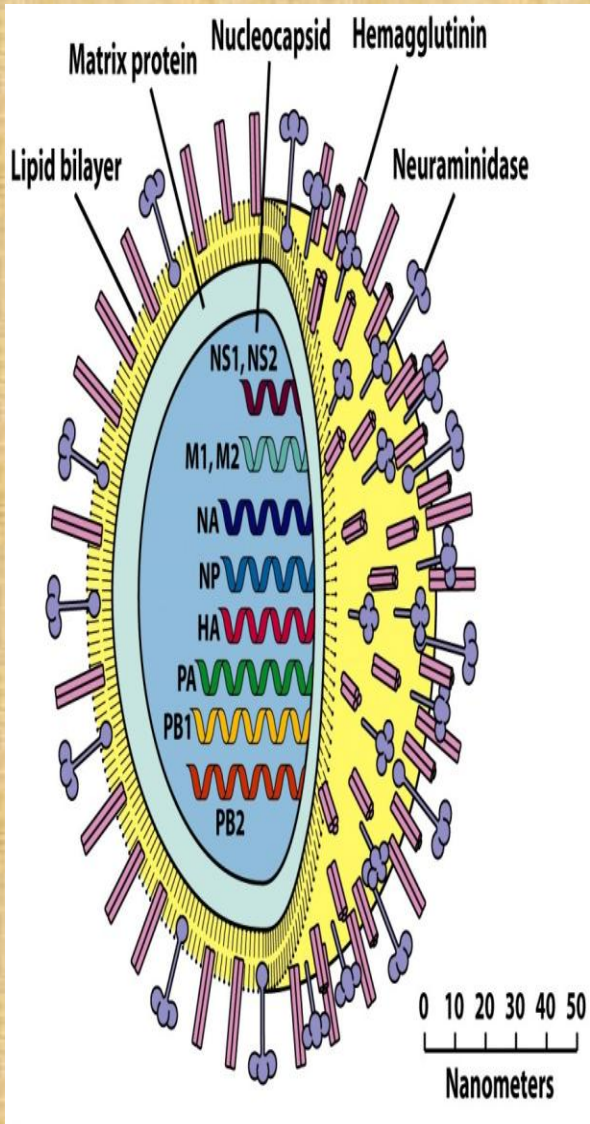


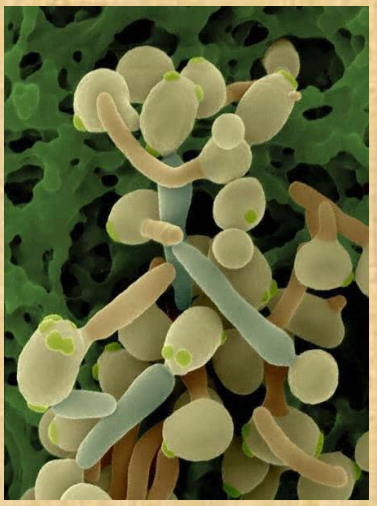
TABLE 18-1 Mechanisms of humoral and cell-mediated immune responses to viruses

Response type	Effector molecule or cell	Activity
Humoral	Antibody (especially secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM, and IgA antibody	Blocks fusion of viral envelope with host cell's plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex
Cell mediated	IFN-γ secreted by T_H or T_C cells	Has direct antiviral activity
	Cytotoxic T lymphocytes (CTLs)	Kill virus-infected self cells
	NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

Defence against fungi

- Opportunistic pathogens
- Antibodies are inefficient
- Neutrophils, macrophages,lymphocytes and probably Nk cells play roles against fungi.
- Th1 response (IFN-γ production to activate macrophages)
- Th17 response (IL-17 production for neutrophils recruitment)
- Systemic disease only in immunocompromised individuals

Aspergillus fumigatus



Candida albicans

- Most fungal infections of healthy individuals resolve rapidly
- Barriers of innate immunity control most fungi
- Mannose-binding protein recognizes some major fungal pathogens
- Patient with neutropenia or defective neutrophil function appear predisposed to hematogenously disseminated infection with yeast like fungi (*Candida* spp) or with filamentous fungi (*Aspergillus*)

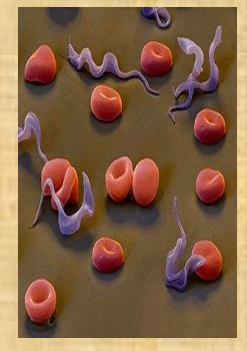
  patients with defective cell mediated immunity (AIDS patients) are predesposed to mucosal candidiasis or hematogenously disseminated infection with *Cryptococcus histoplasmosis*.

Defence against protozoan infections

- Chronic non-symptomatic latent infection
- Antigenic variation, different developmental stages (some are intracellulare other are extracellular)
- Intracellular (*Plasmodium, Trypanosoma, Leishmania, Toxoplasma*)

  Th1 lymphocytes and activated macrophages
- Extracellular (*Entameba, Giardia, Trichomonas*)

  Antibodies
- Clinical manifestation when immune system is compromised or weakend

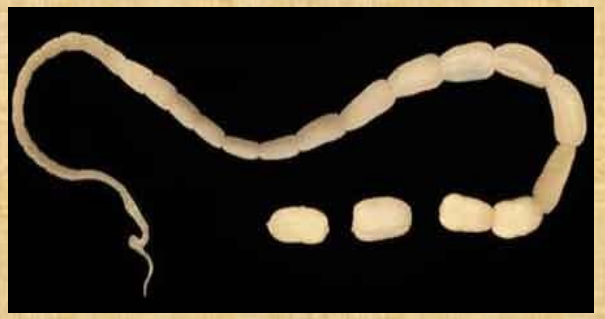


Trypanosoma

Trichomonas

Defence against helminths

- chronic persistent infection (e.g tapeworm, roundworm, pinworms)
- High morbidity, low mortality
- reinfection
- Eosinophils
- Antibody IgE
- later Th1 response (macrophages), CTL.



tapeworm

roundworm

How do Pathogens evade the immune response?

- Pathogens that infect the human body have evolved a number of different techniques for avoiding the immune response.

- These include:
  - Antigenic variation
  - Antigenic mimicry
  - Evading macrophage digestion
  - Hiding in cells
  - Immune suppression
  - Disarming antibodies

Avoiding the immune response

- **Antigenic variation**
  - Some species of protozoan parasites evade immune response by shedding their antigens upon entering the host.
  - Others (e.g. trypanosomes and malarial parasites) can change the surface antigens that they express so that the specific immune system needs to make a new antibody to respond to the infection. This is known as antigenic variation.
- **Antigenic mimicry**
  - This involves alteration of the pathogen's surface so that the immune system does not recognise the pathogen as "non-self".
  - Blood flukes can hijack blood group antigens from host red blood cells and incorporate them onto their outer surface so that the immune system does not respond to the infection.

- **Evading macrophage digestion**
  - Macrophages have an important role in the immune system as they phagocytosis and destroy foreign material. Some microbes (e.g. *Leishmania*) are able to avoid enzymatic breakdown by lysosomes and can remain and grow inside the macrophage – this means they are able to avoid the immune system.
  - Some bacteria can avoid phagocytosis by releasing an enzyme that destroys the component of complement that attracts phagocytes.
  - Other bacteria can kill phagocytes by releasing a membrane-damaging toxin
- **Hiding in cells**
  - Bacteria such as *heliobacter* can invade the epithelial lining of the intestine to multiply and divide, then transfer into neighbouring cells without entering the extracellular space where they would be detected.

- **Immune suppression**
  - Most parasites are able to disrupt the immune system of their host to some extent.
  - HIV is an example of this. It selectively destroys T helper cells, therefore disabling the host immune system.

- **Disarming antibodies**
  - Bacteria such as *Staphylococcus aureus* have receptors on their surface that disrupt the normal function of the host's antibodies.
  - These receptors bind to the constant region (the stem) rather than the normal antigen binding sites. This prevents normal signalling between antibodies and other parts of the immune system such as complement activation or initiating phagocytosis of a bound antigen.

- Virus can evading host defenses by:
  - Block or inhibit production of interferons
  - Inhibition of antigen presentation
  - Evade complement
  - Cause general immunosuppression

Pathogens are not only bad….immunotherapy

Adjuvants

- Derivatives of bacterial cell walls (LPS)
- Bacterial toxins and their non-toxic variants (cholera toxin)

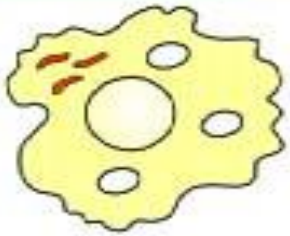
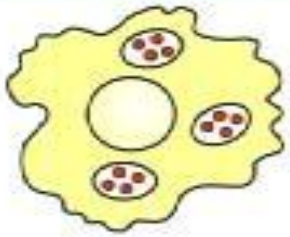
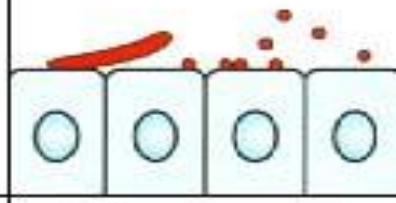
Vectors for antigen delivery

- Attenuated bacterial strains (*Listeria, Salmonella)*
- Bacterial toxins and their non-toxic variants with inserted antigenic epitopes (*B.pertussis* ACT)

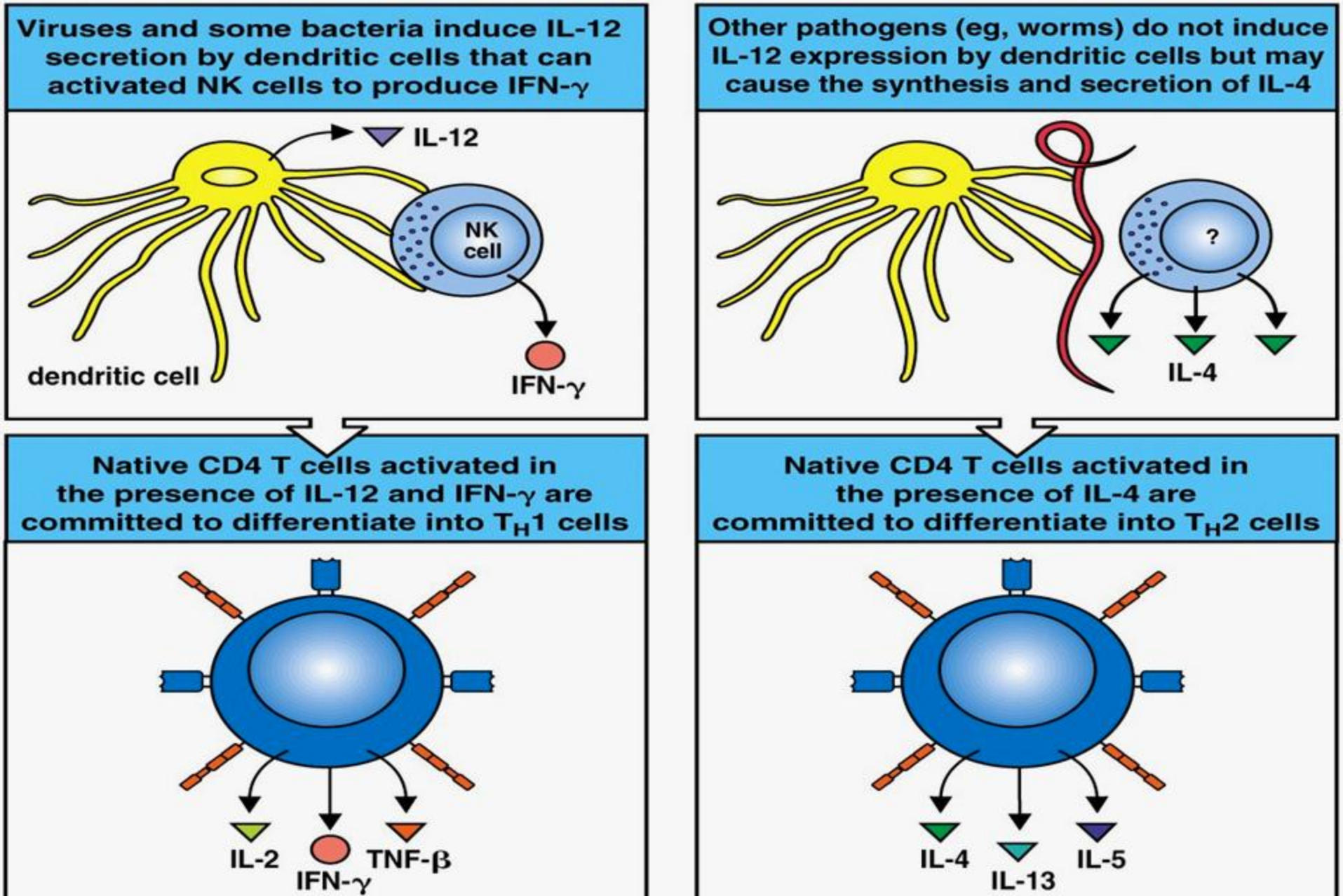
Cytotoxic effects

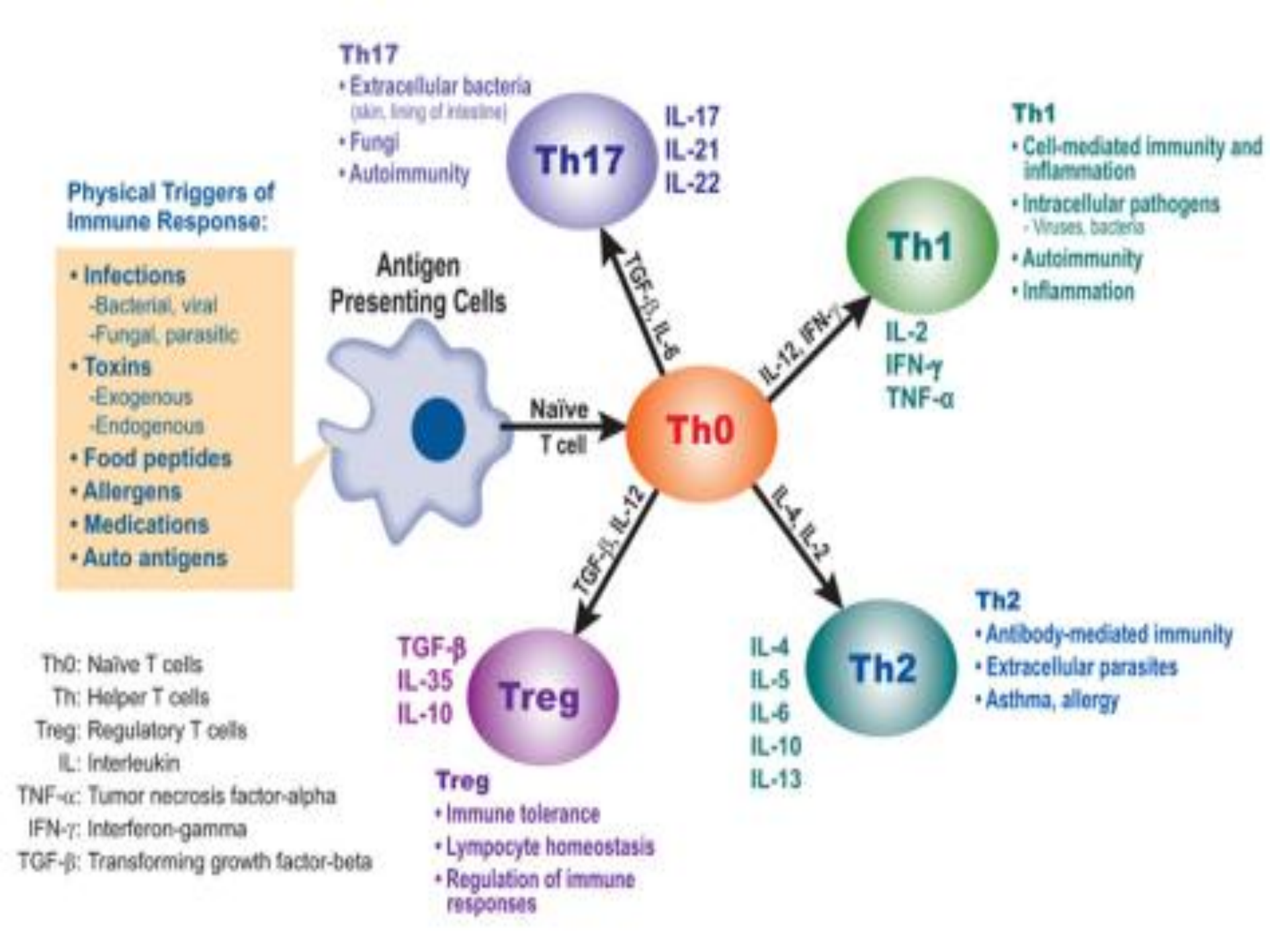
- Immunotoxins containing bacterial toxin bound to an antibody specifically recognizing tumour-associated antigen *(C.diphtheriae* diphtheria toxin*, P. aeruginosa* exotoxin A)

Localization of infection and type of immune response

	Intracellular		Extracellular	
	Cytoplasmic	Vesicular	Interstitial spaces blood, lymph	Epithelial surfaces
Site of infection				
Organisms	Viruses *Chlamydia* spp. *Rickettsia* spp. *Listeria monocytogenes* Protozoa	Mycobacteria *Salmonella typhimurium* *Leishmania* spp. *Listeria* spp. *Trypanosoma* spp. *Legionella pneumophila* *Cryptocccus neoformans* *Histoplasma* *Yersinia pestis*	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* Worms Mycoplasma *Streptococcus pneumoniae* *Vibrio cholerae* *Escherichia coli* *Candida albicans* *Helicobacter pylori*
Protective immunity	Cytotoxic T cells ADCC NK cells	T-cell dependent macrophage activation	Antibodies Complement Phagocytosis Neutralization	Antibodies, especially IgA Inflammatory cells

Infection induced Th1 vs. Th2 responses.




Th17
• Extracellular bacteria
(skin, lining of intestine)
• Fungi
• Autoimmunity
Th17
IL-17
IL-21
IL-22
Th1
• Cell-mediated immunity and inflammation
• Intracellular pathogens
- Viruses, bacteria
• Autoimmunity
• Inflammation
Th1
IL-2
IFN-γ
TNF-α
Physical Triggers of Immune Response:
• Infections
-Bacterial, viral
-Fungal, parasitic
• Toxins
-Exogenous
-Endogenous
• Food peptides
• Allergens
• Medications
• Auto antigens
Antigen Presenting Cells
TGF-β, IL-6
IL-12, IFN-γ
Naïve T cell
Th0
TGF-β, IL-12
IL-4, IL-2
TGF-β
IL-35
IL-10
Treg
Treg
• Immune tolerance
• Lympocyte homeostasis
• Regulation of immune responses
IL-4
IL-5
IL-6
IL-10
IL-13
Th2
Th2
• Antibody-mediated immunity
• Extracellular parasites
• Asthma, allergy
Th0: Naïve T cells
Th: Helper T cells
Treg: Regulatory T cells
IL: Interleukin
TNF-α: Tumor necrosis factor-alpha
IFN-γ: Interferon-gamma
TGF-β: Transforming growth factor-beta