BCHEM 471
Immunity to Infectious diseases

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Study Objectives

- To Describe the various types of immune responses initiated during infection by :
  - Bacteria
  - Viruses
  - Fungi and Parasites

Specific Immune Responses

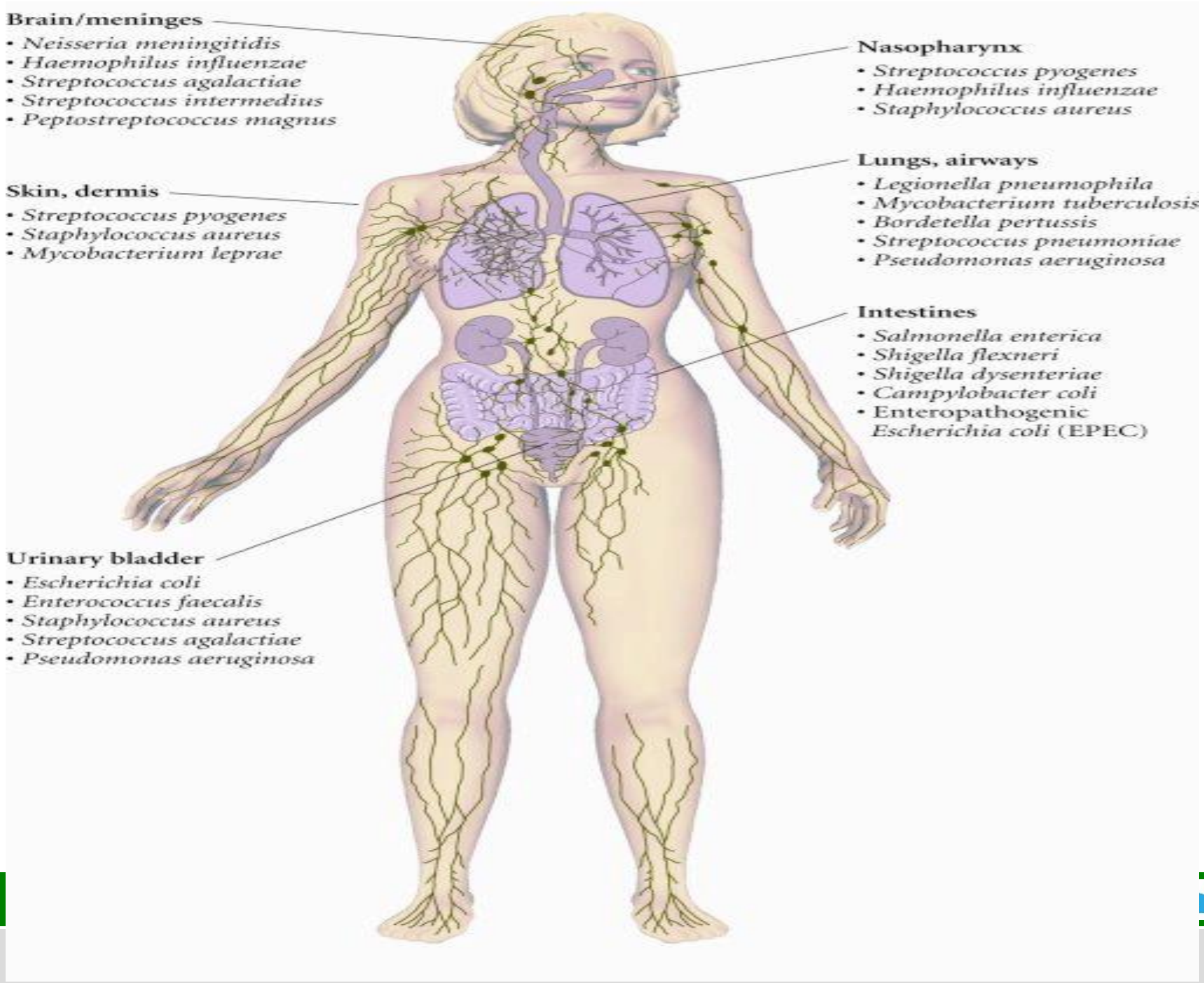
- The immune system has evolved to deal with infectious pathogens.
- Although all pathogens are different from each other, they can be sub grouped by the pattern of the immune response that they evoke.

- In general pathogens may be subdivided as follows:
  - Extracellular bacteria and toxins
  - Viruses
  - Intracellular bacteria
  - Intra and extracellular protozoa
  - Extracellular parasites
  - Encapsulated bacteria

Bacterial Diseases

- Bacteria can Infect any part of the body
- Cause disease due to:
  - Growth of the microbe in a tissue
  - Produce Bacterial factors that are harmful to host
  - Elicit an inflammatory response that causes damage

- but also leads to acquired immunity

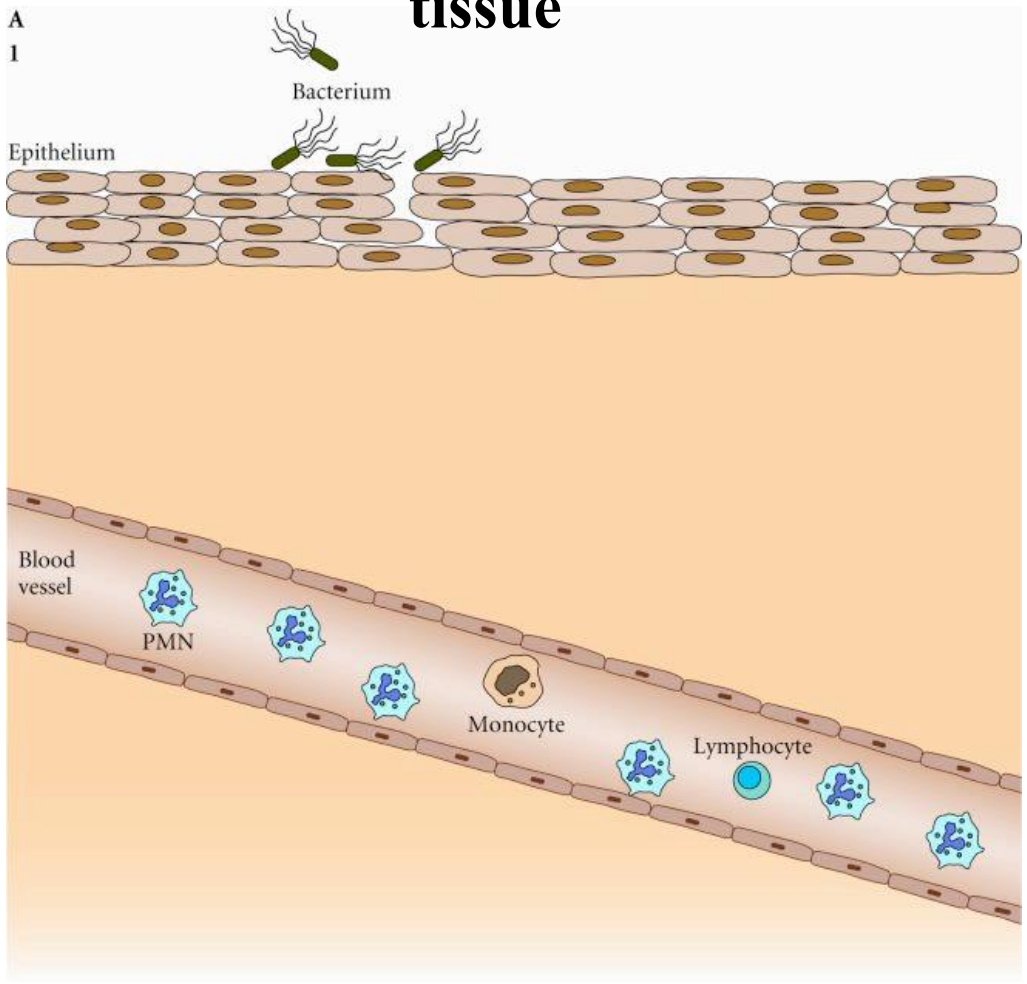


Preferential infection of some bacterial species

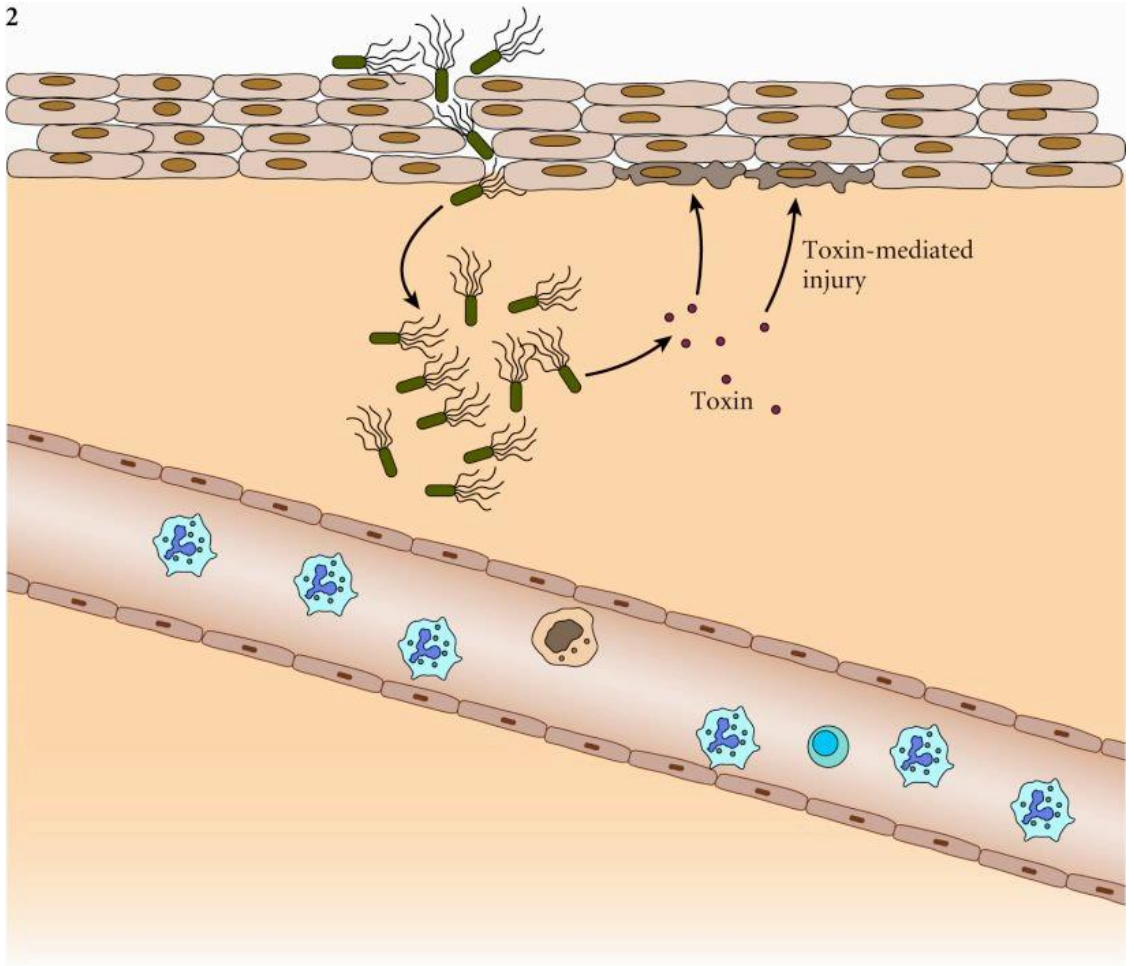
Steps of Bacterial Infection

1. Attachment of bacterium to host tissue
   Persistence and growth called colonization
2. Invasion into deeper host tissues and production of toxins
   - Results in host cell and tissue injury
3. Inflammation at site of invasion
   - Initiated by antibody binding to bacterium
   - Initiated by complement activation at bacterial surface
   - Initiated by wound healing mechanisms
   - All can activate complement pathways that alters vascular permeability and
   activates local macrophage (M!) and neutrophils (PMNs)

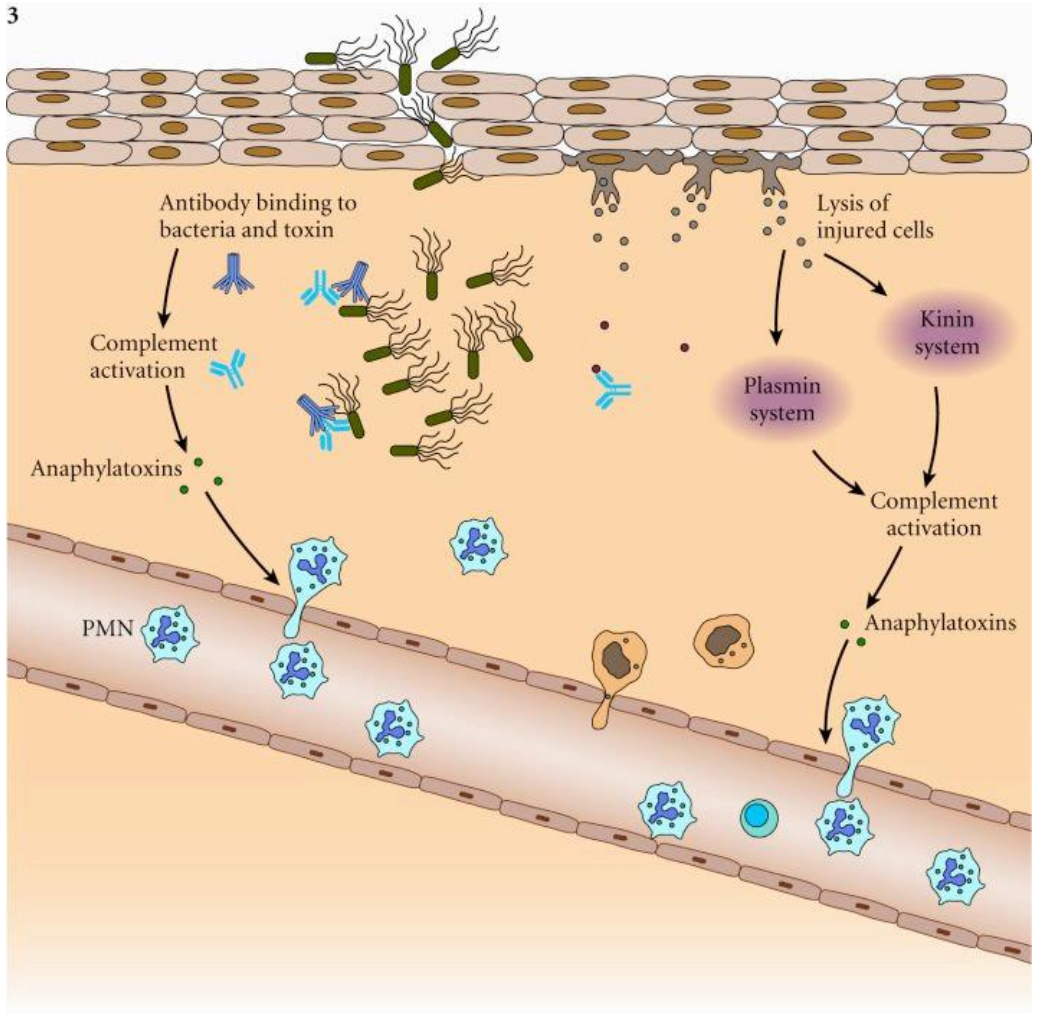
Attachment of bacterium to host tissue



Invasion into deeper host tissues and production of toxins



Inflammation at site of invasion



Factors that promote colonization, entry, and progression to disease

- Bacterial Aliginate
  – Promotes adherence to host tissue
- Bacterial LPS and pilus
  – Promote persistence by resisting complement and phagocytosis
- Bacterial Type III secretion system
  – Deliver enzymes and toxins that
  a. injure host tissues or
  b. diminish host immune responses
  c. Includes signaling proteins, proteases, and superantigens

Innate Immune Effectors and Bacterial Infection

- Major mediators of resistance to bacterial infections
- High numbers of bacteria on skin and mucous membranes
- Usually do not cause disease
- Commensal organisms
- Physical and physiologic barriers prevent entry or destroy quickly after entry

Table 18.1 Innate immune effectors mediating resistance to bacterial infection

Type of mechanism and examples
Physical and physiologic barriers
Skin, sebum, mucosal epithelial cells, mucus, and mucous flow
Enzymatic and protein effectors
Lysozyme, proteases, antimicrobial peptides, iron-sequestering proteins, complement
Recognition of PAMP
TLRs
TLR2 and peptidoglycan and glycopeptides
TLR4 and LPS
TLR5 and bacterial flagella
TLR9 and CpG DNA
Endocytic pattern recognition molecules
Mannose receptor/scavenger protein
CR3
Soluble collectins
Conglutinin
Mannose-binding lectin
Surfactant proteins A and D

Immune System Function and Resistance to Bacterial Infection

- Immunity to extracellular and intracellular bacteria is dependent on different effector immune cells

- Major mediators of resistance to extracellular bacterial infections is ANTIBODIES

- Provide protective immunity by Killing live organisms through
a. Opsonophagocytosis = promotion of complement mediated phagocytosis
b. Neutralizing bacterial toxins to prevent damage and intense damaging inflammatory responses

Immunity to extracellular bacteria by antibodies: gram positive bacteria

- Antibodies and complement result in opsonization via FcReceptors (FcR) or Complement Receptors (CR) on M! and PMN

- Antibody **cannot** activate classical complement pathway resulting membrane attack complex (MAC) because of the thick cell wall, but can do opsonization via CR

- Antibodies can also trigger antibody-dependent cell mediated cytotoxicity (ADCC) by PMN with FcR and CR release proteases, mucleases, lipases, and ROIs

Immunity to intracellular bacteria by cell mediated immunity (CMI)

A. Bacterial antigens present in the cytoplasm of infected host cell
– Processed via endogenous pathway and presented to CD8+ T cells (cytotoxic T lymphocytes or CTLs) on MHC class I

B. Bacterial antigens present in the endosomes of infected host cell
– Processed via the exogenous pathway and presented to CD4+ helper T cells (TH) on MHC class II

C. Some TH cells (TH1) can initiate a DTH response
– Activates M! and kill bacteria and host cell via proteases and ROI

D. Bacterial antigens present on the surface of the infected host cell can be bound by antibodies and targeted for killing by NK cells using ADCC

Bacterial Virulence Factors: How they Thwart Host Immunity

A. Virulence factors are anything that bacteria use to cause disease

- Examples:

– Proteins, glycolipids, carbohydrates, teichoic acids, peptidoglycan, metabolites, enzymes, toxins

- Impede the function of lymphocytes and granulocytes

– Proteins, enzymes, and toxins

- Overstimulate inflammation so normal defenses do not work

– Glycolipids like LPS, cell wall structures like teichoic acids ad peptidoglycan, also enterotoxins and bacterial superantigens

- Prevent phagocytosis

– Carbohydrates like LPS side chains and capsular polysaccharides

- Evade Complement mediated killing

Bacteria Evade Complement mediated killing

- Prevent activated complement components from attaching to the bacterial cell wall or outer membrane
  – Presence of capsule or calyx outside bacterial cell

- prevent CR on phagocytes from binding activated complement on bacterial surface
  – Long or bulky surface components

• Divert activation of MAC from bacterial membrane
– Expression of certain surface proteins

• Cleave, Inactivate, or disassemble activated complement components
– Expression of enzymes

• Prevent membrane insertion of complement complex
– Outer membrane Resistance to insertion
– Secretion of inhibitors

Bacterial Virulence Factors continued…

- Biofilms
  – An organized growth of many microbial cells in a microcolony
  – Establishment of cell-to-cell communication network using soluble factors

- Communication occurs by Quorum Sensing
  – The time when the bacteria has reached a critical mass where the cells in the
  biofilm can detect and respond to each other

• Concentration of signaling molecules is high enough to bind to
receptors and initiate gene transcription of virulence factors results in Bacterial Pathogenesis

Example:
–Dental plaque and the pathology of cavities

Immunity to Viruses

Outline

- Basic Aspects of viral infection and disease
- Innate immune control of viral infection
- Acquired immune control of viral infection
- The general structure of a virus
- How a virus replicates
- Effects of viral replication on host cells
- Viral evasion of host immune responses

Basic Aspects of viral infection and disease

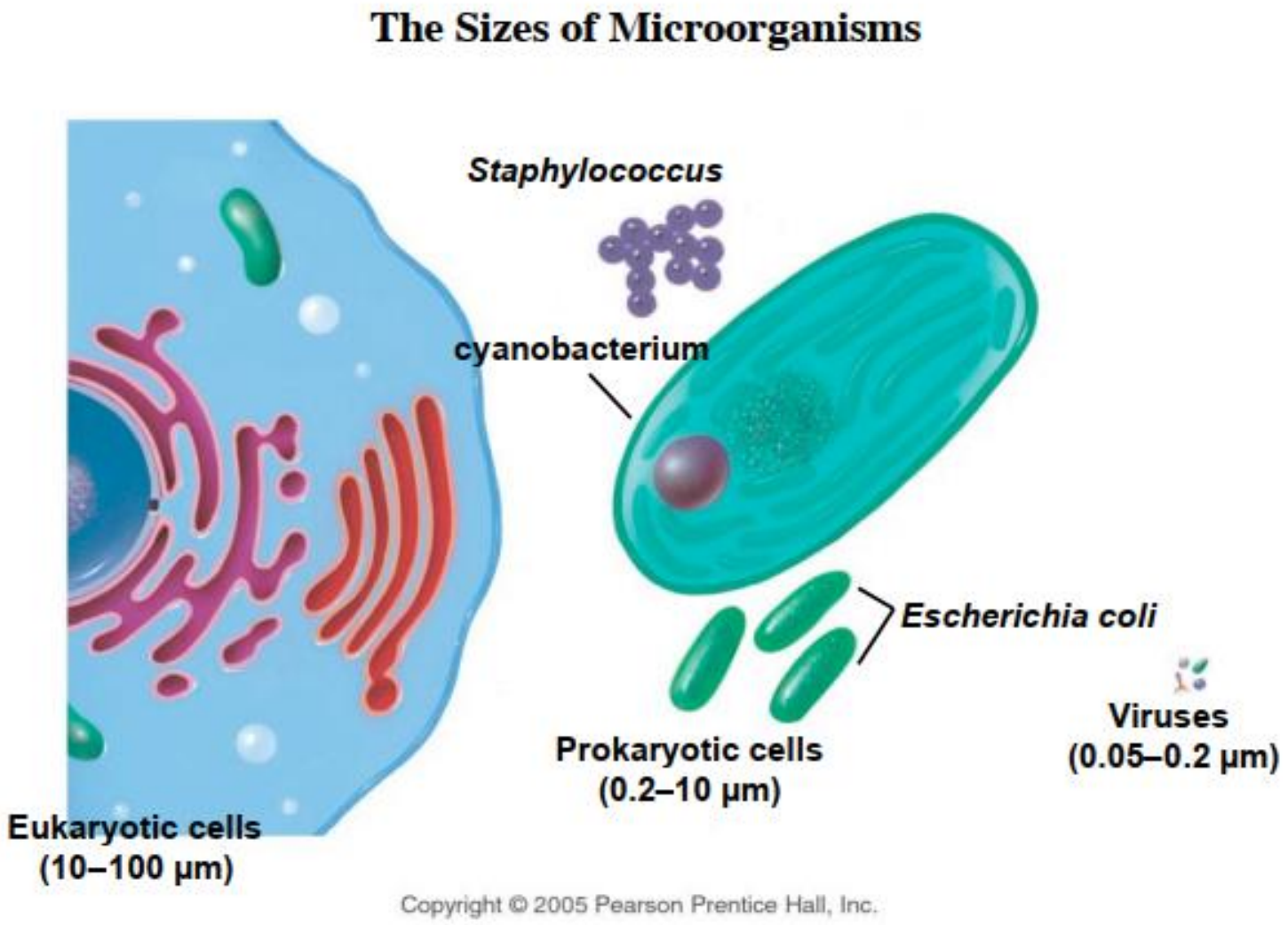
- Virus Consists of a Molecule of DNA or RNA Surrounded by a Protein Coat
  – **The protein coat may be surrounded by a membrane derived from the host cell plasma membrane**

- cannot grow or reproduce without a "Host cell"

host -specific

– **Each type is specialized to infect a certain kind of host cell**

Different Sizes of Microorganisms



Structural Properties of the Virus

- Capsid
  - Encloses the genetic material
  - Nucleocapsid is both capsid and genetic material
  - Protective Proteins surrounding the nucleic acid

- Envelope
  - Not all viruses have one
  - Capsid is surrounded by phospholipid bilayer derived from the host cell
  - Allows virus to leave the host cell without damaging it

• buds off
– Can be cytoplasmic membrane or nuclear membrane bilayer
– Host cell proteins are present in envelope making virus appear to be “self”

• Viral nucleic acid
– DNA or RNA
– Double or single stranded

Morphology of Viruses

• Structures of viruses of different families are separated into groups on the basis of

a. whether they are enveloped or nonenveloped

b. and whether there genome is RNA or DNA,

c. double-stranded or single-stranded

Different forms of viral RNA and DNA

- RNA can be linear
  - Single stranded
  - Double stranded

- DNA can be linear and circular
  - Single stranded
  - Double stranded

- DNA can be linear with covalently linked ends
  - Double stranded

- DNA can be linear with covalently linked terminal proteins
  - Double strand

General Information about Virusus

- Viruses come in a variety of shapes
  - **Determined by the nature of the protein coat**
  - **Determined by whether they use host cell plasma membrane**

- Are Host-Specific
  - **Example: HIV infects "helper T cells" of human immune systems**

- Viral Infections Are Difficult to Treat
  - **Mutation rates are high**
  - **Viruses hide within cells**

Basic Aspects of viral infection and disease

- Noncellular and nonliving submicroscopic entities
- Viral respiratory infections:
  - Infants in first year >6 on average
  - Adults usually have 3 to 4 a year

– Signs and symptoms
- Fever
- Increased secretion of fluids
- Sneezing, coughing
- Sore throat
- Malaise
- Headache

- Gastrointestinal viruses (usually Norwalk viruses)

– Signs and symptoms
- Abrupt onset of nausea, cramps, vomiting, and diarrhea

Stages in Viral Life Histories

- Stage 1: The virus attaches to the host cell
- Stage 2: The viral nucleic acid enters the cell
- Stage 3: The cell synthesizes proteins specified by the virus' genes

- Stage 4: The cell replicates the virus' DNA or RNA

- Stage 5: The new viral protein and DNA or RNA assembles into
new viruses

- Step 6: The new viruses are released from the cell

Host cell responses to viral infection

- Cytopathic effects

– Extensive damage to host cell organelles

- Intracellular inclusions

– Massive inclusion bodies in the nucleus or cytoplasm of infected cell

– Clusters of viral particles or products

- Cell fusion
  – Multinucleated giant cell - syncytium
  – Multiple infected cells fuse together

- Host cell metabolic effects
  – Inhibition of host cell's protein synthesis
  – Replicating viral particles comandeer the host cell's transcription and
  translation machinery

Table 19.1 Some common diseases caused by viruses in humans

Virus family	Virus	Diseases
Herpesviridae	Herpes simplex virus type 1	Cold sores
	Epstein-Barr virus	Infectious mononucleosis, Burkitt's lymphoma
	Varicella-zoster virus	Chicken pox, shingles
Poxviridae	Variola virus	Smallpox
Hepadnaviridae	Hepatitis B virus	Hepatitis
Papovaviridae	Papillomavirus	Warts
Orthomyxoviridae	Influenza virus	Respiratory diseases
Togaviridae	Rubivirus	Rubella
Paramyxoviridae	Mumps virus	Mumps
	Morbillivirus	Measles
	Respiratory syncytial virus	Respiratory diseases
Rhabdoviridae	Lyssavirus	Rabies
Retroviridae	HIV	AIDS
Coronaviridae	SARS virus	SARS

EMERGENCE OF NEW VIRAL DISEASES

- Mutants
  - High and rapid rate of viral replication
  - Influenza pandemic in 1918/19 KILLED tens of millions of people
  - 2003 new form of coronavirus caused severe acute respiratory syndrome (SARS)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that COVID-19. Started in Wuhan China in 2019.

- Ability of viruses to
  – infect every type of cell from bacterial to human cells
  – Rapid generation times
  – Large numbers of particles produced
  – High mutation rates

- Can generate new variants in very short periods of time

Innate immunity plays a key role in resistance to viral infection

- Viral replication rapidly stimulates innate immunity
- Interferons (IFN) are antiviral factors expressed by many cells when virally infected
- Natural Killer (NK) cells recognize virally infected cells and kill them via cytotoxicity

• Complement proteins on Membrane Attack complex(MAC) can disrupt the viral envelope
– Phospholipid bilayer stolen from the host cell

• Complement can opsonize viral particles for phagocytosis by Macrophages(M)

Interferons (IFN) have antiviral properties

- Type I and type II IFN
- Unrelated biochemically but both have antiviral effects
- IFN can control viral infections by
  – Binding receptors on infected or uninfected cells
- prevents further spread of the virus

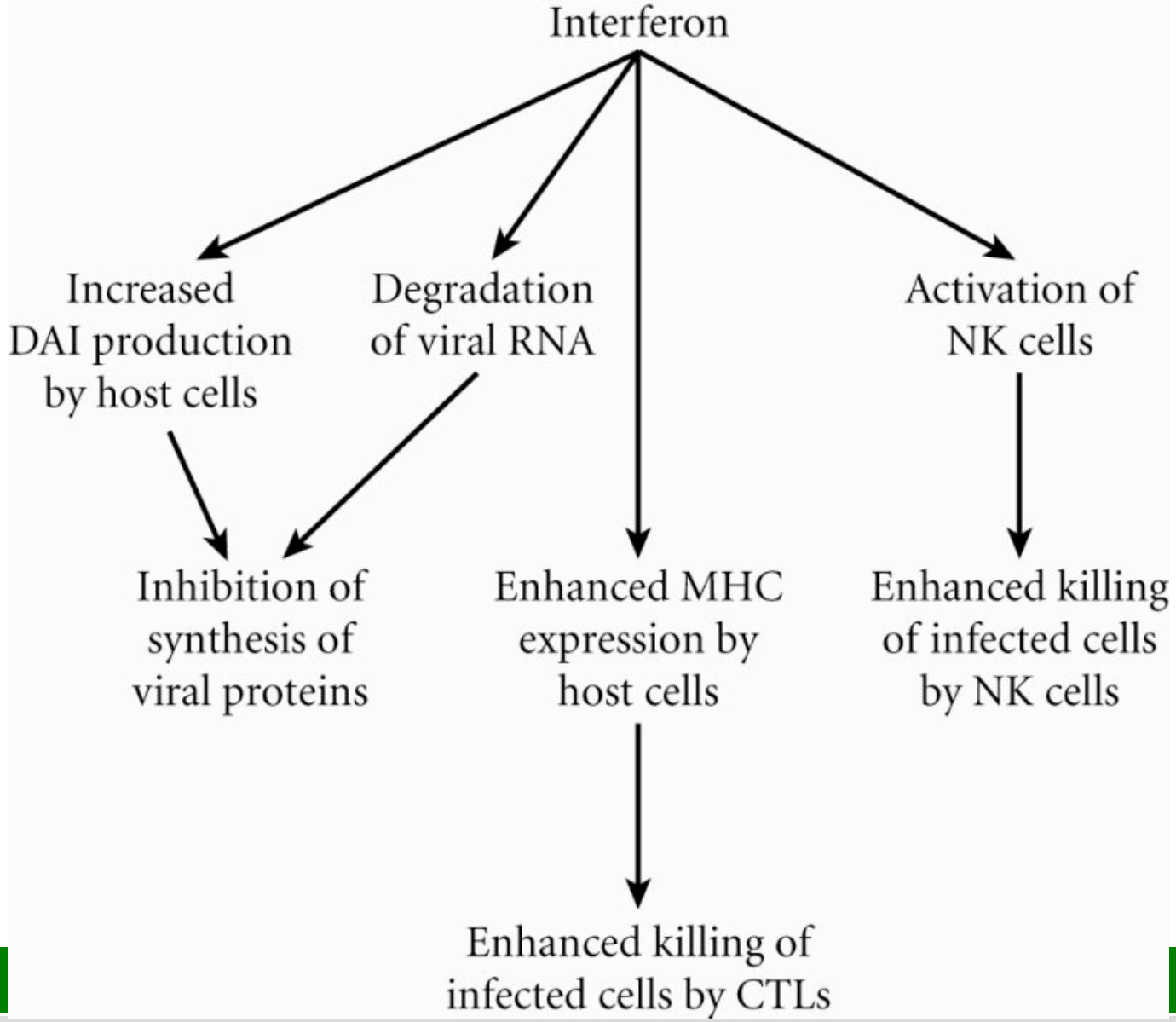
• IFN binding to IFN-R
– inhibits synthesis of viral proteins
– Increase expression of MHC class I molecules

• Enhances the destruction of infected cells by Cytotoxic T lymphocytes (CTLs)

• prevents uninfected cells from being killed by NK cells

• IFN binding to Receptors on NK cells increases their ability to destroy
cells that have decreased MHC class I expression and/or are coated with antiviral antibodies

Interferons (IFN) have antiviral properties



Natural Killer (NK) cells can control viral infections

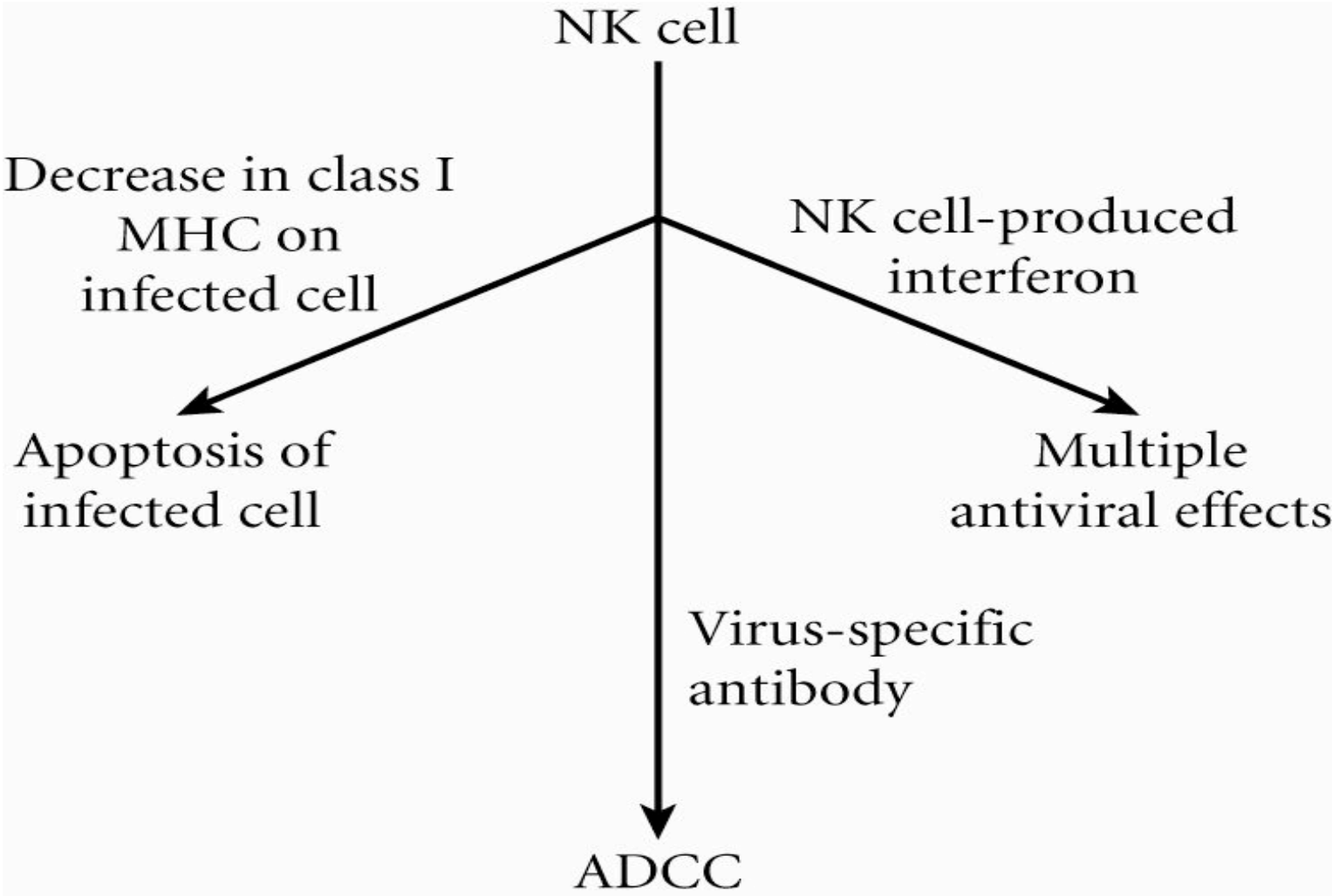
- The virally induced MHC class I downregulation – triggers NK cells to kill the infected cells

- Recognize infected cells coated with antiviral antibodies using Fc receptors (FcR)

• and kill them through antibody dependent cell mediated cytotoxicity (ADCC)

• Produce increased amounts of IFN-γ
– Binds IFN-R to prevent production of virus

Natural Killer (NK) cells can control viral infections



Viruses and Acquired Immunity

- Antibody mediated immunity or humoral immunity
- Cell mediated immunity (CMI)
- Delayed Type Hypersensitivity (DTH) reactions

Viruses and Acquired Immunity…….

- Antibody mediated immunity or humoral immunity

- Antibody mediated antiviral responses

- Antibodies directed at viral surface antigens are the most
effective in controlling and clearing viral infections

- Antigens are usually proteins

- Virus can escape antibody binding by mutating the viral antigen gene thereby changing the antigen
– Influenza virus genes HA and NA are highly variable due to
high mutation rate of the encoding genes.
– HIV rapidly changes the gp160 gene that encodes the gp41 and
gp120 surface glycoproteins

Viruses and Acquired Immunity…….

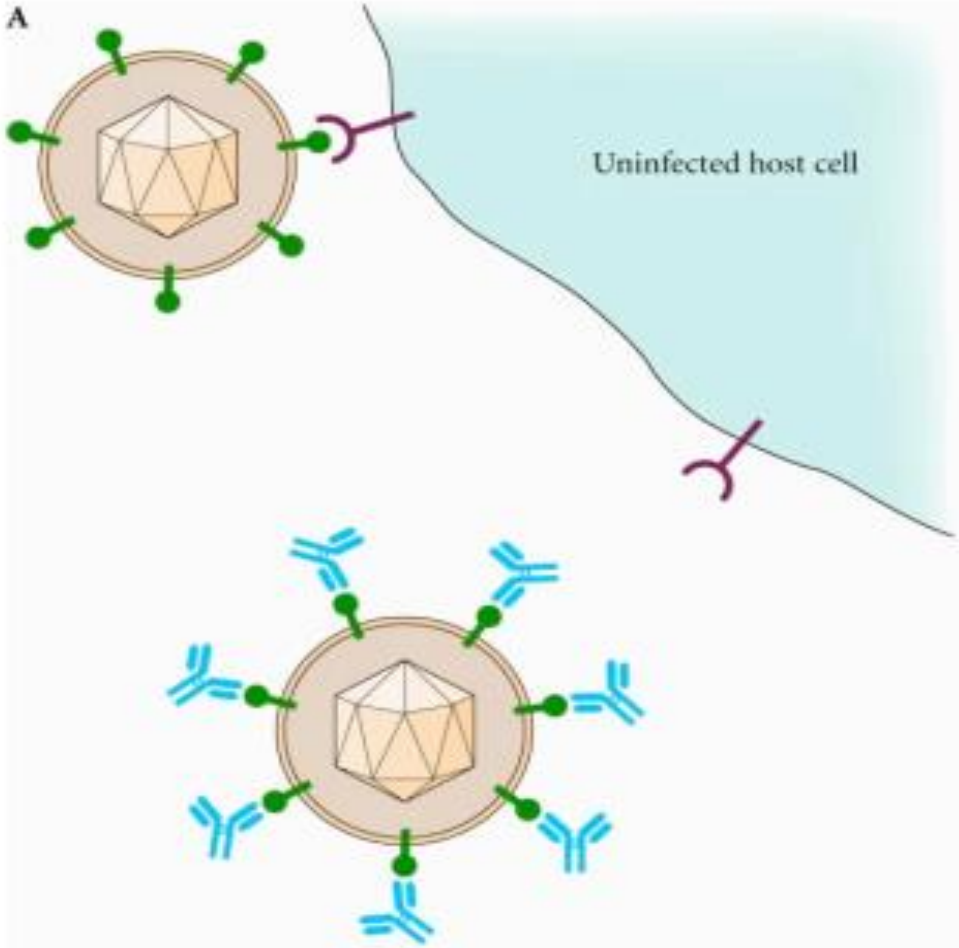
- Antibody dependent control of viruses
  – Example HIV

- Antibodies can prevent a viral ligand from binding to the host cell receptor and entering the host cell

- If a virus succeeds in infecting a cell, the antibody can recognize viral antigens on the membrane of the infected cell.

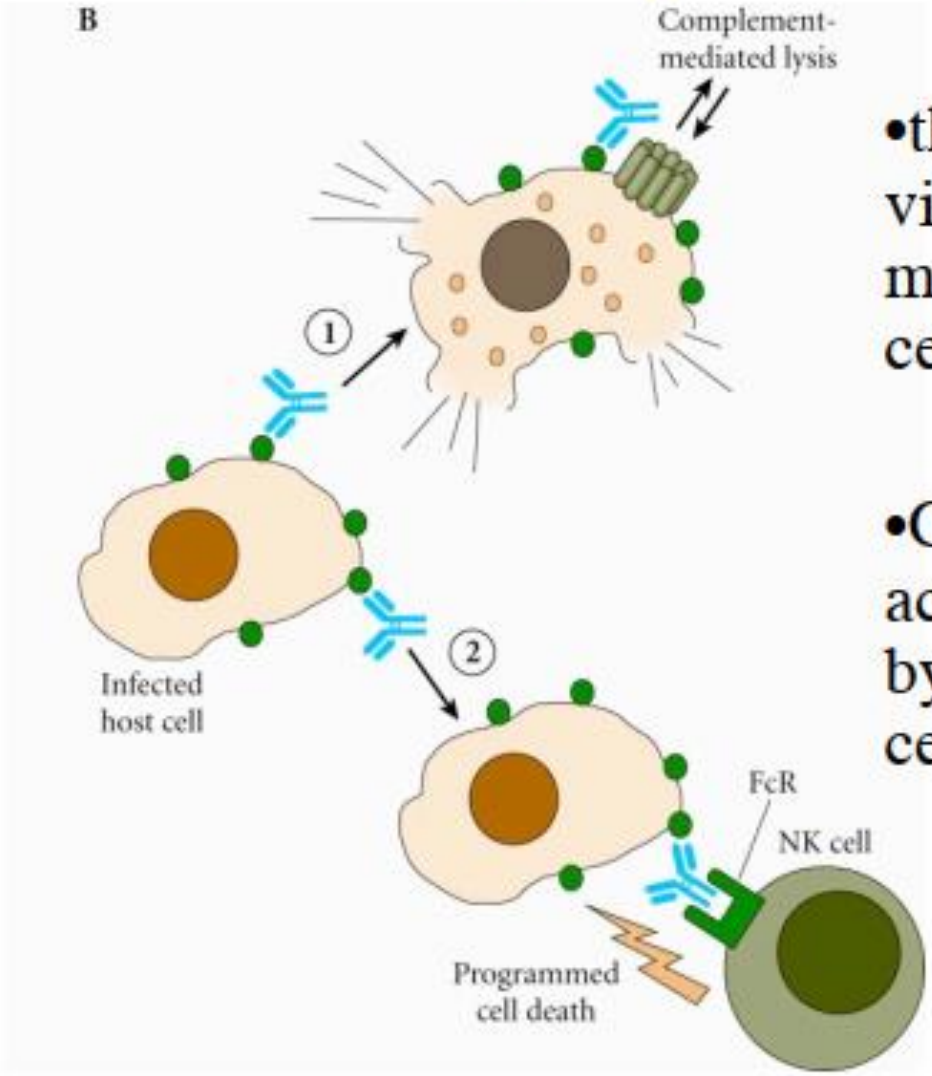
- Cell is lysed through activation of complement or by ADCC by activating NK cells expressing FcR

Viruses and Acquired Immunity
Antibody dependent control of viruses



- Antibodies (BLUE)
- can prevent a viral ligand (GREEN)
- from binding to the host cell receptor (PURPLE)
- and entering the host cell

Viruses and Acquired Immunity
Antibody dependent control of viruses



- the antibody can recognize viral antigens on the membrane of the infected cell.

- Cell is lysed through activation of complement or by ADCC by activating NK cells expressing FcR

Viruses and Acquired Immunity, Cell dependent control of viruses

- Antiviral Cellular immune responses are

a. required to inhibit the further spread of virus in the infected cells and

b. essential for clearing the host of virus once infection has been established

- Effector cells are Cytotoxic T lymphocytes (CTLs)

Viruses and Acquired Immunity…….

- Cytotoxic T lymphocytes (CTLs)

A. Induce cell death 2 ways
– Perforin/granzyme pathway
– Fas/ FasL pathway

Both induce infected cell to apoptose

Antiviral CTL responses occur in 4 phases

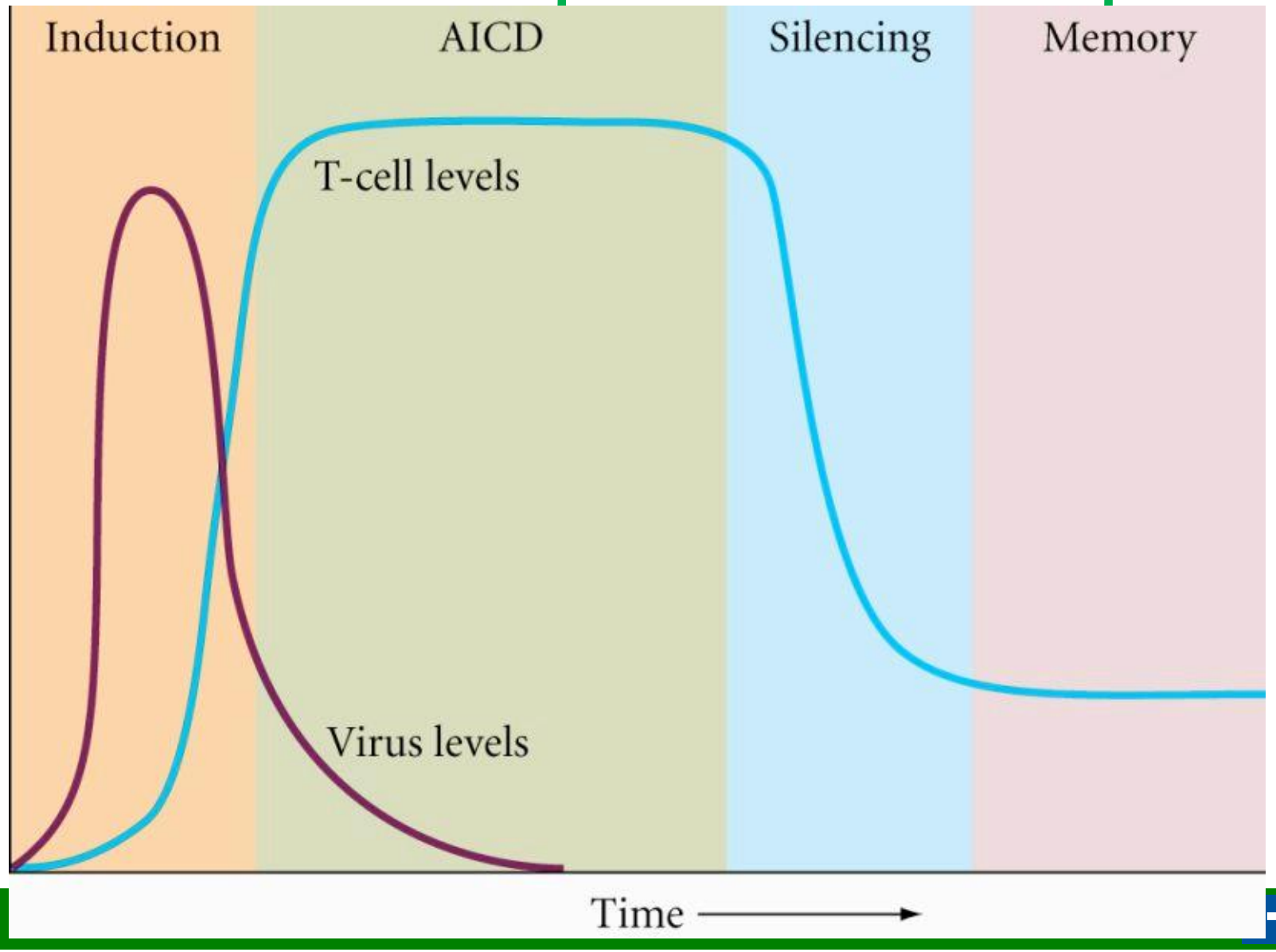
1. Induction phase
– CD8+ precursor T cells proliferate, differentiate into effector cells, and attack and kill virally infected cells

2. Activation-induced cell-death (AICD) phase
– Activated CTLs responding to another encounter with viral antigen undergo apoptosis

3. Silencing phase
– Loss of AICD but continuation of apoptosis in virus-specific CTLs

4. Memory phase
– Some of the virus-specific activated CTLs remain viable and stable as memory cells
– Mostly dormant or resting - but have ability to recognize specific viral antigens, proliferate, and lyse infected cells upon reencounter with the same viral antigen

Antiviral CTL responses occur in 4 phases



Evasion of Host Antiviral Immune Defenses

• Dormancy/latency and the Proviral state
– Insert into host genome and remain dormant/latent

Papilloma virus, herpes simplex virus,

• Regulation of molecules involved in apoptosis and antigen presentation
– Escape antibody or complement mediated destruction

• Viral FcR or CR compete for the real thing

• Disruption of antiviral cytokines
– Produce viral cytokines that decrease immune response

• Poxviruses encode soluble IFN-R that bind the IFN and prevent binding to the real thing on NK and CTLs (no IFN-R binding = no activation)
• Viral antigen mutation
– Antigenic drift
– Antigenic shift

Evasion of Host Antiviral Immune Defenses……

- Viral antigen mutation - example Influenza HA and NA

– Antigenic drift
- Random point mutations in HA and NA render them invisible to memory B and T cells

- Usually results in mild disease since many epitopes will still be the same as the "old" virus

– Antigenic shift

• Occurs when segmented RNAs encoding HA and NA are reassorted between different viral strains infecting the same cells

• This is only possible because the influenza genome consists of 8 separate RNAs

• Implications for the flu vaccine….

• All epitopes are essentially “new” and invisible to memory B and T cells

• leads to severe disease and dissemination

Immunity to Parasites and Fungi

- Overview of parasitic diseases
- Immune response to parasitic infections
- Immunity to malaria
- Immunity to schistosomiasis
- Immune effectors in parasitic infections
- How parasites evade the immune response
- General features of fungal pathogens
- Immunity to fungal infections

Overview of parasitic diseases

• Parasites live in or on a host and cause harm to the host while they derive benefits from the host

• Specifically the Protozoa and the Helminths
– Protozoa are single celled eukaryotic organisms

• pathogenic protists
– Helminths are multicellular eukaryotic organisms (worms)

- Nematodes or roundworms
- Trematodes or flukes
- Cestodes or tapeworms

Overview of parasitic diseases…..

Protozoa are single celled eukaryotic organisms

- The most serious and intensely studied protozoal infections include :
- Malaria
  – *Plasmodium falciparum*

- Leishmaniasis
– *Leishmania donovani or L. major*

- Trypanosomiasis
– *Trypanosoma brucei or T. cruzi*

- Toxoplasmosis
– *Toxoplasma gondi*

Overview of parasitic diseases……

Disease	Major Species	Mode of Transmision
Malaria	P. falciparum, P. Vivax	Female Anopheles Mosquito bite
Leishmaniasis	L. donovani, L. Major	Sand fly bite
Typanosomiasis	T. brucei, T. cruzi	Tsetsefly bite
Toxoplasmosis	Toxoplasma gondii	Infective stages in cat feaeces, undercooked meat
Lymphatic Filariasis	W. bancrofti	Mosquito bite

T cells and Cytokines Regulate Immune Responses in Parasitic Infections

- T cells are critical to control all parasitic infections
- Do not provide protective immunity against reinfection
- Are required to control parasitic infection

• Genetically deficient mice lacking B and T cells and athymic mice with few T cells are

– unable to control infections and

– develop overwhelming parasite burdens that are fatal

T cells and Cytokines Regulate Immune Responses in Parasitic Infections…..

- Development of tissue injury is often due to
  – Inappropriate immune response
  – rather than insufficient immune response

- T cells are usually responsible for immune mediated injury and disease progression

- TH cell subsets (TH1 and TH2) were discovered through
  – dissecting disease resolution versus disease progression
  – and immune-mediated injury in parasitic infections

TH cell subsets and their cytokines regulate immune responses to parasites

• Expansion of TH1 or TH2 cells in response to infection is dependent on
– Nature of the invading organism
– Genetics of the host

• Host genetic importance demonstrated in inbred mouse strains where difference in genetic background can determine whether an infection is
– Harmless or Lethal

• First shown with *Leishmania*
– Induction of TH1 leads to disease resolution
– Induction of TH2 leads to disease progression

TH cell subsets and their cytokines regulate immune responses to parasites….

Many Studies have shown:

- Activation of TH1 lymphocytes is usually necessary for the destruction of protozoa

- Activation of TH2 lymphocytes occurs in Helminth infections
  - Characterized by increase in eosinophils and mast cells
  - and upregulated IgE levels

- TH2 bias has been studied in murine models and humans infected with schistosomes or filarial nematodes

- For tissue helminths, it is unclear whether the TH2 response benefits the host or the parasite

- For Gut nematodes, it is clear that TH2 cytokines are necessary for clearance of the parasites

IL-12 drives TH1 responses

• IL-12 initiates TH1-dependent cell-mediated immune responses

• IL-12 Is produced by phagocytic cells and B cells
– in response to infection with protozoan parasites

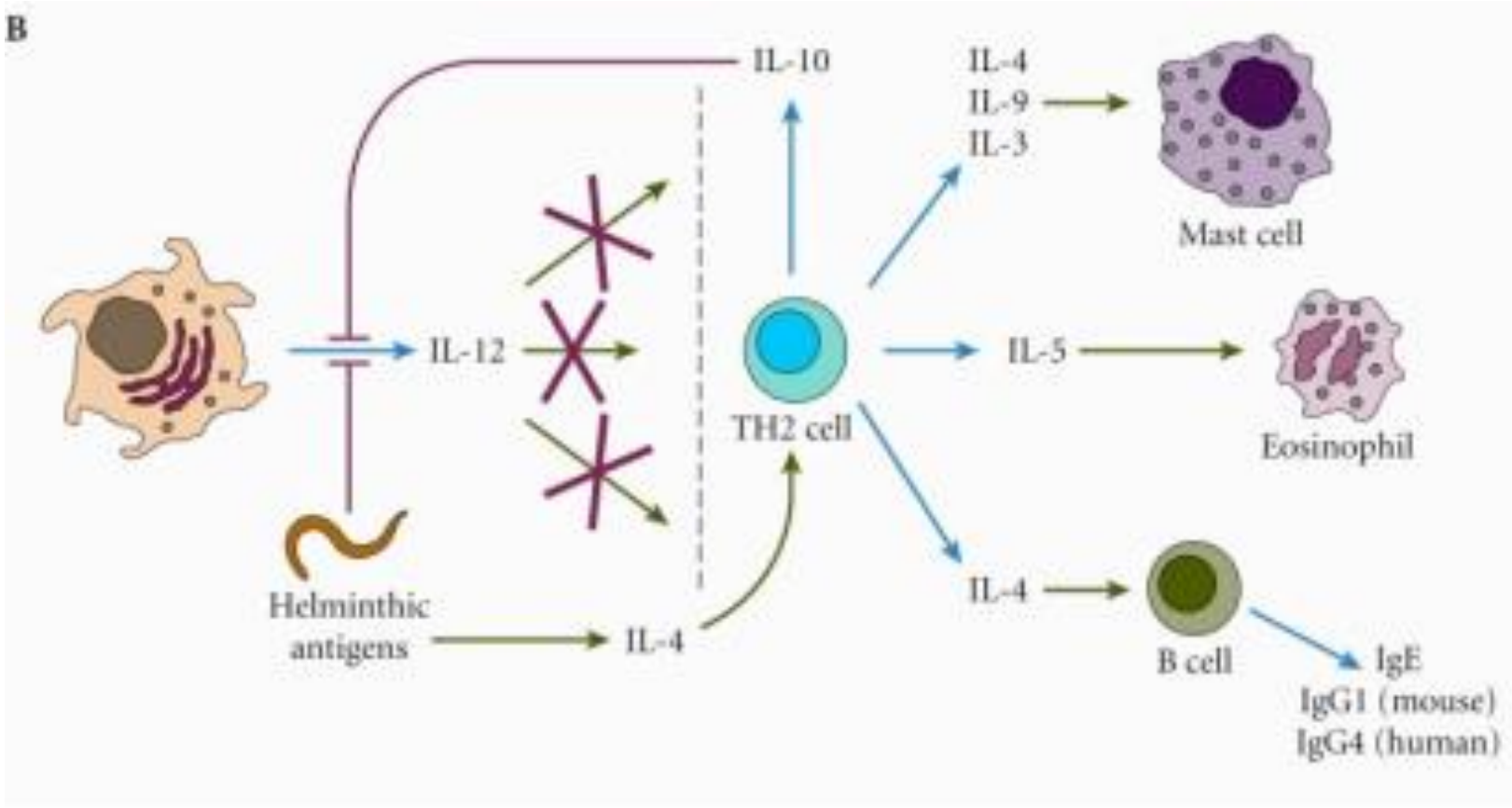
- IL-12 is a Critical component in the early response to infection that drives TH1 cell expansion

- IL-12 Directly stimulates the production of IFN-γ
– by T cells and NK cells

IL-12 and parasite infection

- Helminthic Antigens induce the production of IL-4
- IL-4 drives TH2 development
- Helminthic parasites do not induce production of IL-12
- and may directly block production of IFN- γ
- TH2 cells produce IL-10 which directly blocks IL-12 production

IL-12 and parasite infection…..



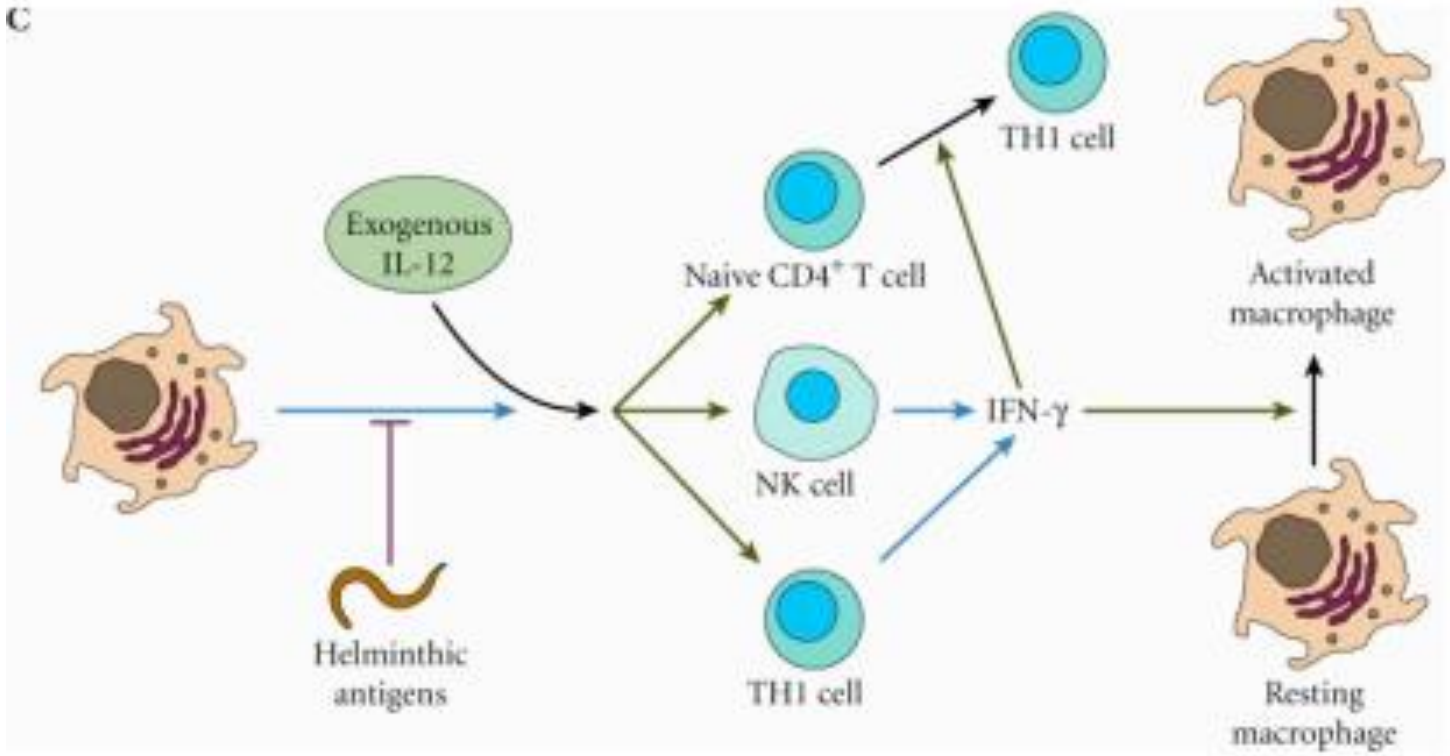
IL-12 and parasite infection….

When exogenous IL-12 is added to helminthic infections:

- Normal production of TH2 cells is prevented

- TH1 cell development follows pathway of protozoan parasitic infection

IL-12 and parasite infection….



IFN

- For intracellular protozoan parasites:
  – IFN-γ Is the major cytokine responsible for disease resolution
  – Because it activates macrophages

- Inbred mouse strains BALB/c and C57BL/6
  – BALB/c: produces IL-4 and TH2 response to *L. major*
  – C57BL/6: produces IL-12 and TH1 response to *L. major*

- TH2 is not protective and mice die (no IFN -γ)

- TH1 is protective and mice clear infection and remain resistant to reinfection (yes IFN -γ)

IL-4 initiates TH2 response to Helminths

- Hallmarks of Helminthic infection :

– Elevated IgE

– Elevated eosinophils in blood and tissue

– Mast cell hyperplasia

Above are Induced by TH2 responses

- IL-4 is critical for inducing TH2 response
- Cells that can produce IL-4 include specialized T cells like NK1.1 and mast cells, basophils, and eosinophils

- After initial induction, TH2 cells take over IL-4 production
– And IL-5, IL-6, IL-9, and IL-13

- It is not yet known what helminthic signal caused initial production of IL-4

TH2 responses to Helminths clears parasites

- BALB.K: IL-4 / TH2 response / no IFN-γ/ clears parasite

- B10.BR: IL-12 / TH1 response / yes IFN-γ / chronic infection

- Give BALB.K mice anti-IL-4 antibody
  – Binds up all IL-4 so it cannot work
  – No TH2 response that usually downregulate TH1 response
  – Get a TH1 response and yes IFN-γ
  – Mice have chronic infection

- Give B10.BR mice anti-IFN-γ antibody

– Binds up all IFN so it cannot activate M!

– No TH1 response to downregulate TH2 response

– Mice clear the parasites

TH2 responses to Helminths

- Universal feature of worm expulsion (nematode species) is the TH2 response

- The specific TH2 cytokines that are needed for expulsion differ for different parasite species

- Represents different effector mechanisms that mediate the expulsion of the different parasite species

Fungi

- Humans encounter, ingest, and inhale fungi daily
- Only several hundred of the estimated 10^5 fungal species cause human disease
- Fungi cause a broad range of diseases with syndromes that involve superficial, tissue invasive, and allergenic manifestations

Structure

- Fungi are eukaryotic, saprophytic organisms with a rigid cell wall

- The fungal cell wall contains polysaccharide and lipid moieties that activate immune responses

- The cell wall is exterior to the plasma membrane

- arranged in layers:

-the innermost layer typically consists of chitin

-N-acetylglucosamine polymer

-adjacent external layer : This is formed by immunoreactive β-(1,3) and β-(1,6) glucans, which are concealed by many fungi

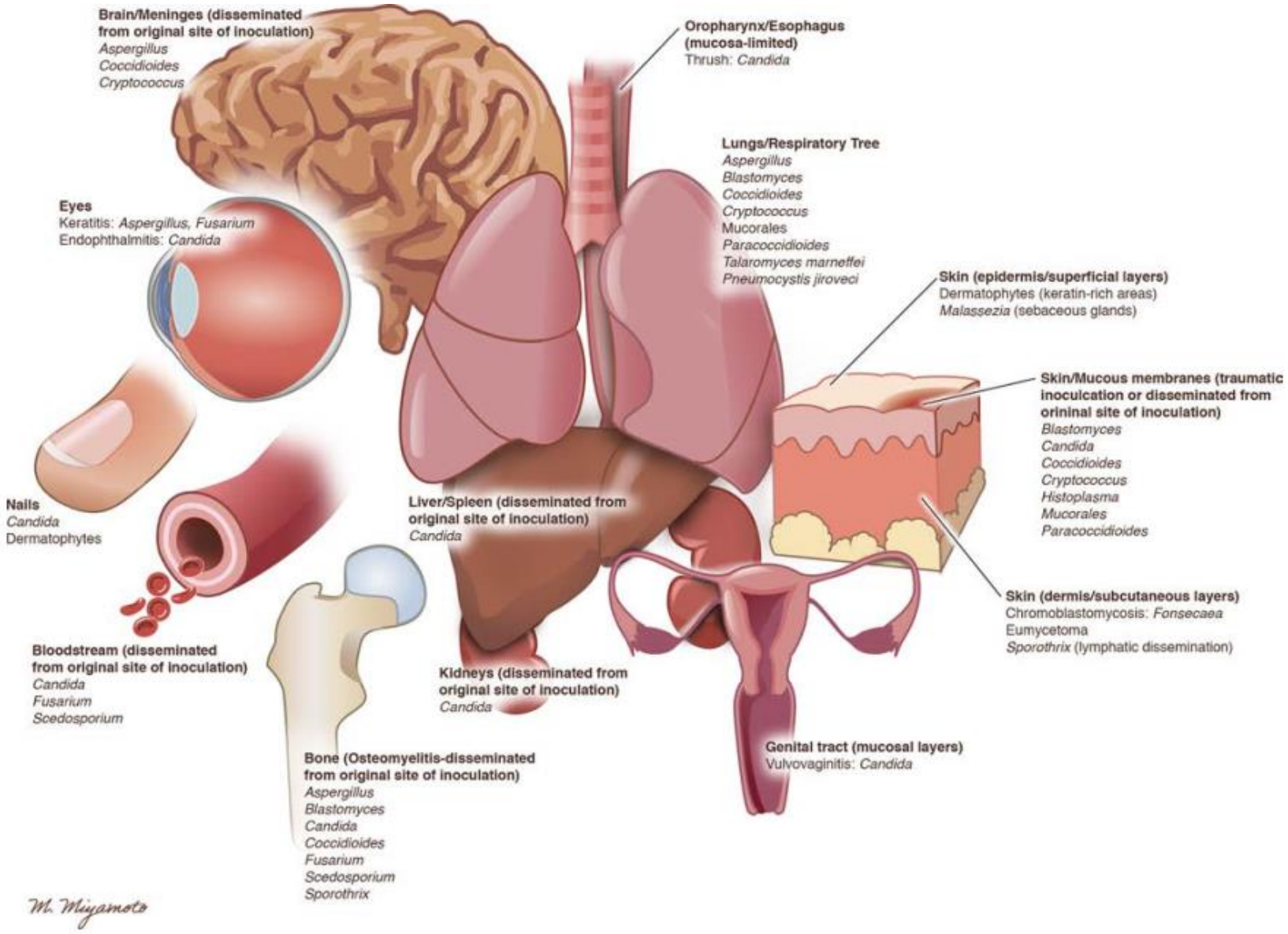


Figure 1. Human fungal diseases. The figure depicts the anatomic sites that are most commonly affected by the fungal genera listed below each organ system. At several sites, fungal disease occurs due to inoculation at the site. For example, humans inhale infectious conidia or desiccated fungal cells of all genera listed under lungs and respiratory tree. For other sites, such as the liver, spleen, and blood stream, disease is the result of dissemination of the indicated fungus from the initial inoculation site. Illustrated by Mao Miyamoto.

Fungi Immune activation

- Innate
- Fungi bind antibodies, complement, surfactant, and soluble pattern recognition receptors at portals of entry.

- Opsonization by these mechanisms promotes fungal uptake and innate immune activation by a wide range of phagocytic and signaling receptors

- Highly conserved fungal cell wall components and nucleic acids trigger innate immune activation in macrophages, dendritic cells, and neutrophils, as well as in epithelial cells

- Toll like receptors

-The ligation of fungal cell wall polysaccharides and nucleic acids activates murine Toll-like receptors(TLR1-4, 6, 7, and 9) signaling. Although deficiency of the TLR adaptor protein MyD88 renders mice susceptible to C. neoformans and C. albicans and delays A. fumigatus clearance fungal infections are not a prominent clinical phenotype in humans with MyD88 deficiency

Fungi Immune activation……

- C-type lectin receptors

-Three immunoreceptor tyrosine-based activation motif (ITAM)-dependent C-type lectin receptors (CLRs; Dectin-1, Dectin-2, and Mincle) activate innate and adaptive antifungal responses.

- Simultaneous CLR and TLR activation by fungal antigens augments NF-$\varkappa$B responses in macrophages and dendritic cells.

- Adaptive

-TLR and CLR signaling induces MHC class II, co-stimulatory molecule, and cytokine expression by antigen-presenting cells that dictate T cell differentiation

-Th1 and Th17 cells are the principal T helper subsets that contribute to protective immunity to several pathogenic fungi

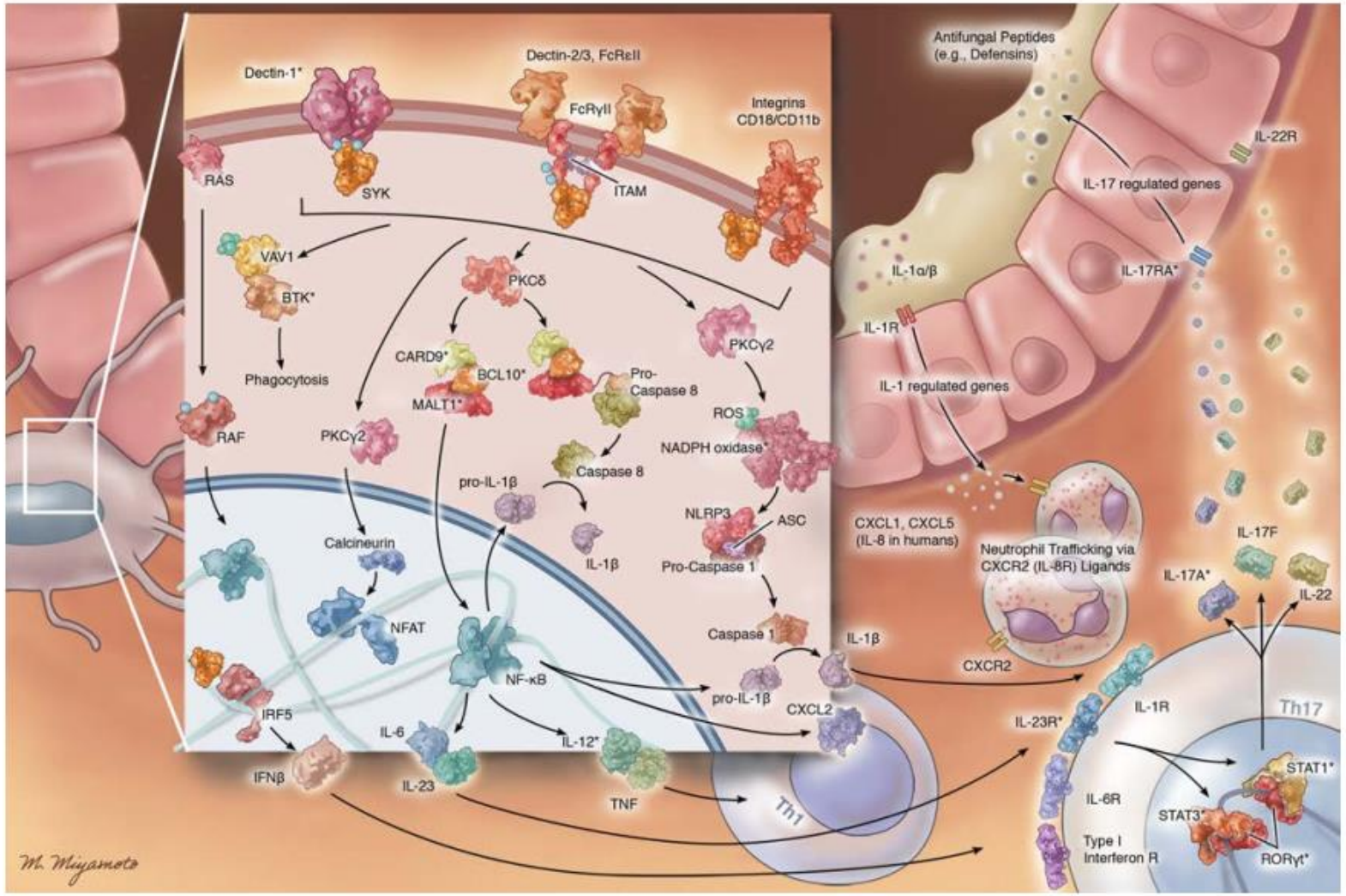


Figure 2. Model of fungus-induced CLR signaling in antifungal defense. At the site of inoculation, particulate fungal polysaccharides bind C-type lectin receptors (CLRs) and Fc receptors (FcRs), resulting in SYK activation via ITAM signaling in the receptor tail, the FcRγ signaling adaptor, or integrin receptor activation. The ensuing PKCδ and CARD9 activation is critical for caspase-1 and caspase-8 activity, MAP kinase signaling (not shown), NF-κB activation, and cytokine production. SYK-dependent PLCγ2 activation is linked to NADPH oxidase assembly and calcineurin-dependent NFAT activation. Dectin/SYK signaling controls IRF5-dependent IFN-γ production. VAV1 and BTK can interact with dectin-1 to mediate phagocytosis of *Candida albicans* in macrophages. BTK

Immune Reaction to fungal infection

- The field of antifungal immunity has rapidly advanced

- Important areas of future research include:

- elucidation of the role of epithelial surfaces in fungal virulence

- antifungal defense and the intercellular crosstalk underlying innate and adaptive antifungal immunity.

Thank You

BCHEM 471
Hypersensitivity

Amma Larbi(PhD)

Introduction

- Certain human disorders are attributed to activity of the immune system.

- These disorders are commonly known as hypersensitivities, states of increased immune sensitivity that are mediated by antibody or cellular factors.

- The general nature and symptoms accompanying the reaction depend upon whether antibodies or sensitized T-lymphocytes are involved.

- When antibodies are involved, the reactions fall under the heading of immediate hypersensitivity. When T-lymphocytes are involved, the reactions are characterized as delayed hypersensitivity.

- Hypersensitivity reaction: a condition in which the normally protective immune system has a harmful effect on the body

- Hypersensitivity reactions known generally as allergic reactions are made in response to inherently harmless 'environmental' antigens such as pollen, food, and drugs.

- Hypersensitivity reactions are classified into four types by Coombs and Gell .

Four Main types of hypersensitivity

- Type-I hypersensitivity reaction: IgE antibody mediated
- Type-II hypersensitivity reaction: Antibodies mediated
- Type-III hypersensitivity reaction: Antigen-antibody complex mediated
- Type-IV hypersensitivity reaction: Activated T-cell and cytokines mediated

- Immediate hypersensitivity reactions include :

-anaphylaxis

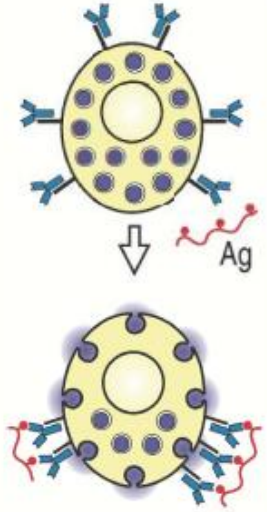
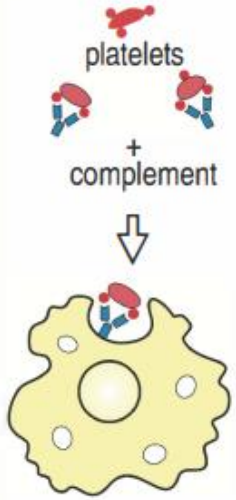
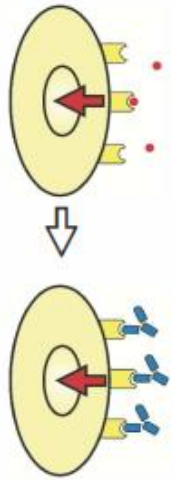
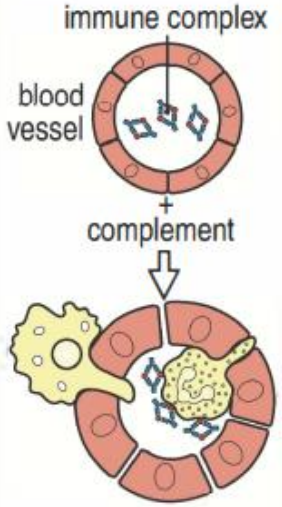
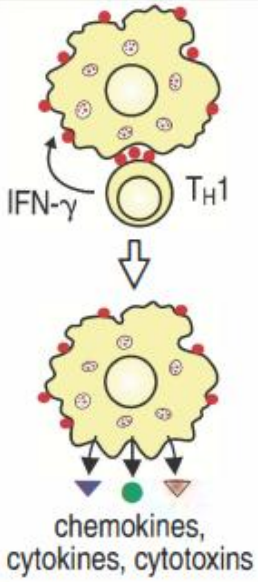
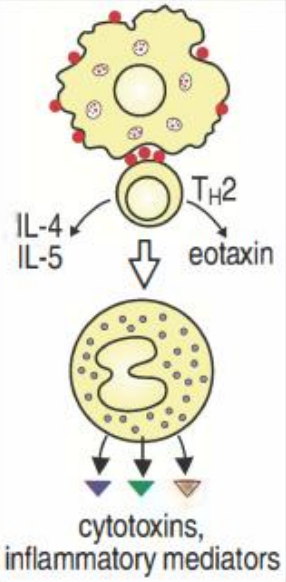
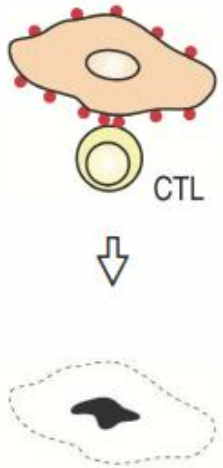
-allergic reactions

-cytotoxic reactions

- immune complex reactions

- Delayed hypersensitivity reactions

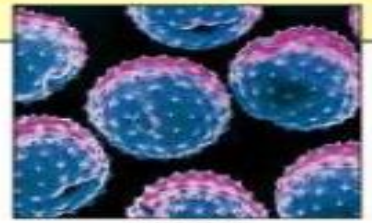
-contact dermatitis or infection allergies

	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, phagocytes	Macrophage activation	IgE production, eosinophil activation, mastocytosis	Cytotoxicity
							

Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
e.g., house dust mites


pollen


house dust mite

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins


wasp


drugs

Ingested materials

Food
Orally administered drugs


peanuts


shellfish

Contacted materials

Plant leaves
Industrial products made from plants
Synthetic chemicals in industrial products
Metals


poison ivy


nickel coin

Immediate hypersensitivity reaction

- Immediate hypersensitivity reaction is mediated by humoral antibody and manifests within minutes to few hours.

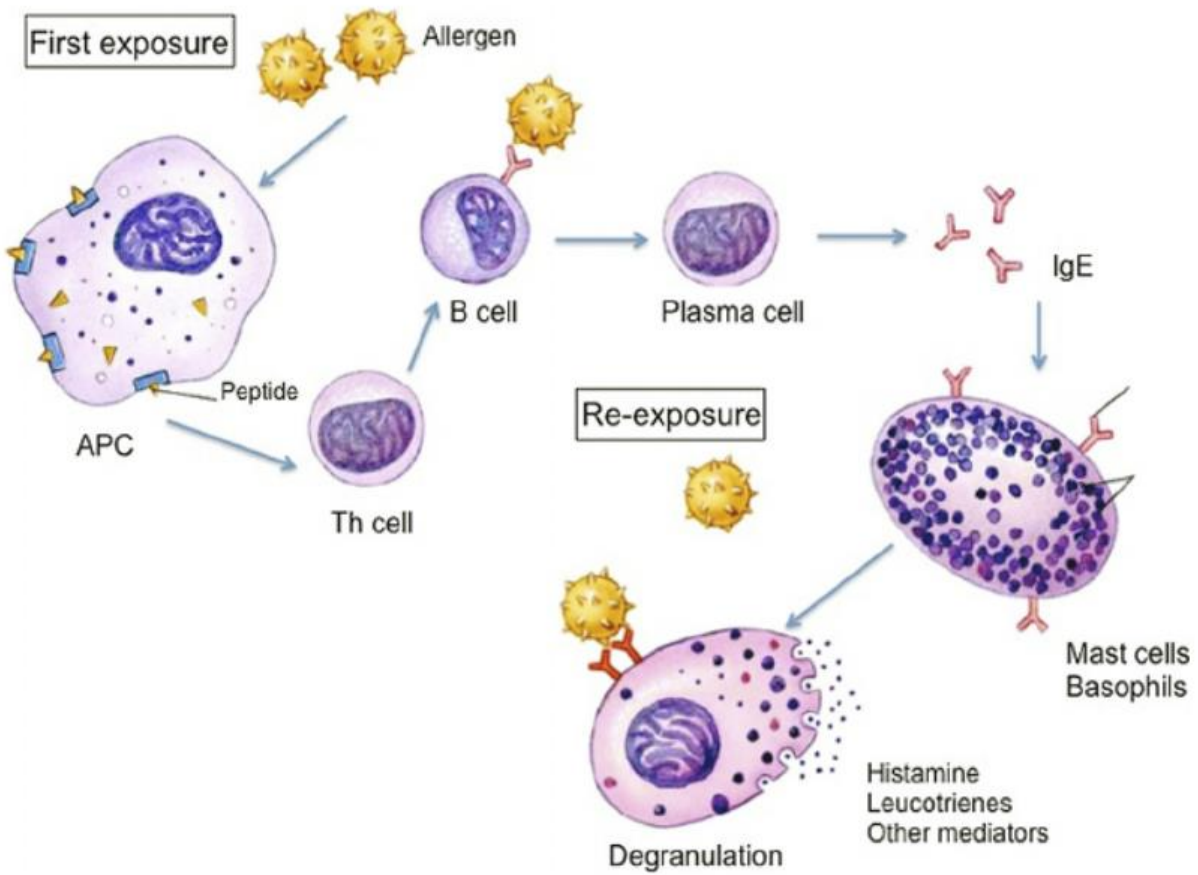
- The anaphylactic reaction initiated by antibody or Ag-Ab complex are referred as immediate hypersensitivity because it occurs within minutes or few hours after a sensitized host encounter with antigen

- Type-I, II and III hypersensitivity reaction are immediate

- This type depends on nature of the antigen, the frequency and route of antigen contact, and the type of antibody reacting with the antigen.

- The initial dose of antigen is referred to as the **sensitizing dose**. This exposure is followed by a latent period and then a later dose of the same antigen, called the **eliciting dose or shocking dose**. The shocking dose sets off the hypersensitivity reaction, resulting in tissue damage.

Type 1 hypersensitivity



Mechanism of Type I hypersesnsitivity reaction:

Production of IgE antibody:

- When antigen (allergen) enters into host, production of antibody begins.
- At first allergen is processed and presented by antigen presenting cells (APCs) to CD4 T cells.
- Activated CD4 t cells divides to form T helper cell and memory cell. T helper produces IL4.
- At the same time B cell bind to antigen in presence of APC and IL4 and gets activated.
- Activated B cells divide to form plasma cells and memory cells.
- Up to this step, mechanism is similar to that of normal humoral immune response. The difference between Type I hypersensitivity and normal immune response is that the plasma cell produces IgE antibody instead of Ig M or IgG.

Sensitization:

- Fc region of IgE antibody has receptor on the surface of tissue mast cells and blood basophils. So the IgE antibody binds to FcRI of mast cells and basophils.

- This binding of IgE to mast cell and basophil is known as Sensitization and the mast cells and basophils are said to be sensitized.

- **Shocking dose of antigen:**

When the same antigen (allergen) enter into same host for second time in life, antigen cross linked with Fab region of IgE molecules on the surface of mast cell or basophils.

- **Degranulation of mast cell:**

The cross-linking of antigen (allergen) to IgE antibody causes degradation of mast cell and basophils releasing various pharmacological active chemicals such as histamine, heparin, serotonin, cytokines, leucotriene, prostaglandin etc.

- **Anaphylatic reaction:**

-These active chemical mediators acts on surrounding tissue producing various symptoms of allergy such as vasodylation, smooth muscle contraction, mucus production, sneezing, etc.

-The allergic reaction may be localized or systemic depending upon types of allergen.

Clinical manifestation of Type I hypersensitivity reaction:

- Clinical symptoms ranges from life threatening conditions such as systemic anaphylaxis and severe asthma to localized reaction such as hey fever and eczema.
- **A. Systemic anaphylaxis:**

It is a shock like and often fatal state, which is usually initiated by allergen directly into blood stream or absorbed from gut or skin.

symptoms include:

-Labored breathing

-Drop in blood pressure

-Smooth muscle contraction

-Bronchiole constriction

-Suffocation

B. Localized hypersensitivity:

It is limited to specific target tissue or organs, often involving epithelial surface at the site of allergen entry.

- The tendency to manifests hypersensitivity reaction is inherited and is called atopy.
- Atopic allergy includes wide range of IgE mediated disorders such as:

-Hey fever (allergic rhinitis)

-Asthma (allergic or intrinsic)

-Food allergy

-Atopic dermatitis (eczema)

Type II hypersensitivity

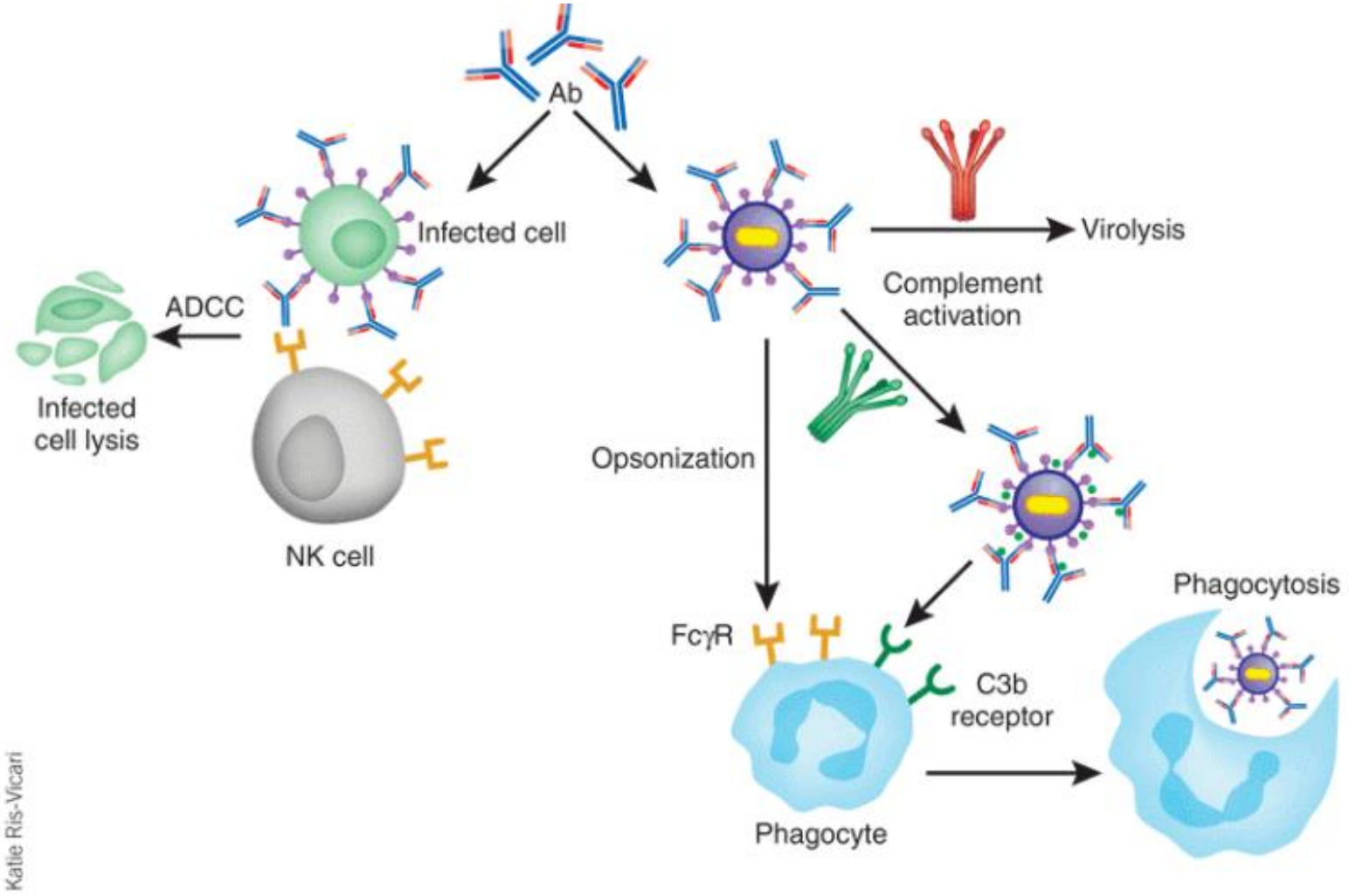
- In this hypersensitivity reaction, specific antibody (IgG or IgM) bound to cell surface antigen and destroy the cell. If the cell is microorganism, killing of cell is beneficial to host. However in Type II hypersensitivity, the cells are ones own RBC.

The killing of cell can occurs by one of the three mechanisms:

-Complement mediated cell lysis

-Antibody dependent cell mediated cytotoxicity (ADCC)

-Opsonization


Ab
Infected cell
ADCC
Infected cell lysis
NK cell
Virolysis
Complement activation
Opsonization
FcγR
C3b receptor
Phagocyte
Phagocytosis
Katie Ris-Vicari

Examples

A. Blood transfusion reaction:

B. Hemolytic disease of new born (Erythroblastosis fetalis):

- Hemolytic disease of newborn develops when maternal IgG antibodies specific for fetal blood group crosses placenta and destroy fetal RBCs.

-The consequences of such transfer of antibody can be minor, serious or lethal to fetus.

-Serious hemolytic diseases of new born develops when Rh –ve mother conceive Rh +ve fetus, which causes erythroblastosis fetalis.

C. Drug induced hemolytic anemia:

-Certain drugs such as penicillin, cephalosporin and streptomycin can absorb non-specifically to protein on surface of RBC forming complex similar to hepten-carrier complex.

Type III hypersensitivity

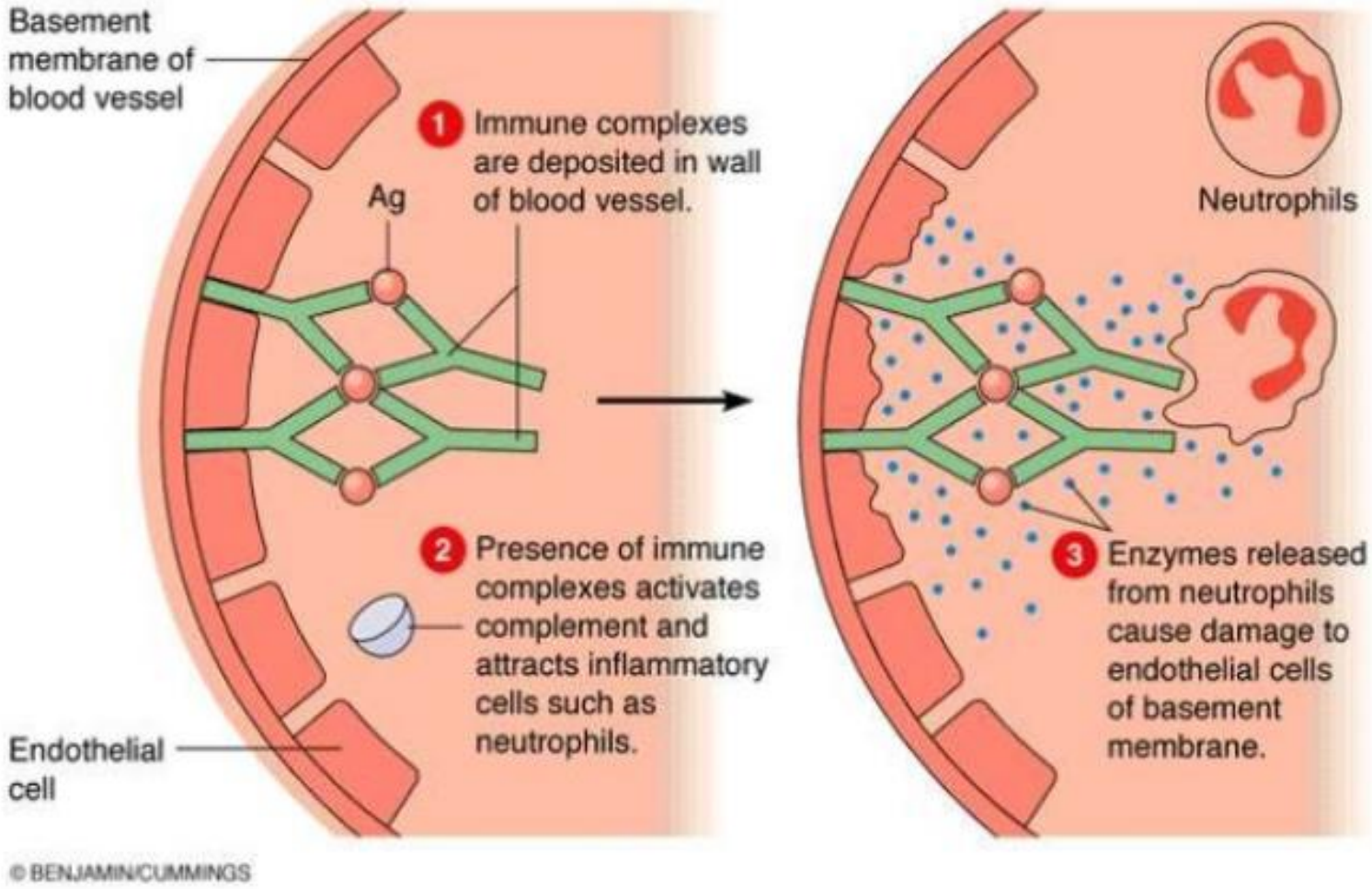
- The reaction of antibody with antigen generates immune complex. In most of the cases, these immune complexes are removed from blood circulation. Some immune complexes are removed by phagocytic action of phagocytic cells in blood. Most other immune complexes are first carried by blood to spleen where they are destroyed by macrophages. Complement system is also needed for removal of immune complexes from blood to spleen.

- In some cases large amount of immune complexes are formed and deposited on various body parts and leads to tissue damage resulting in Type III hypersensitivity reaction.

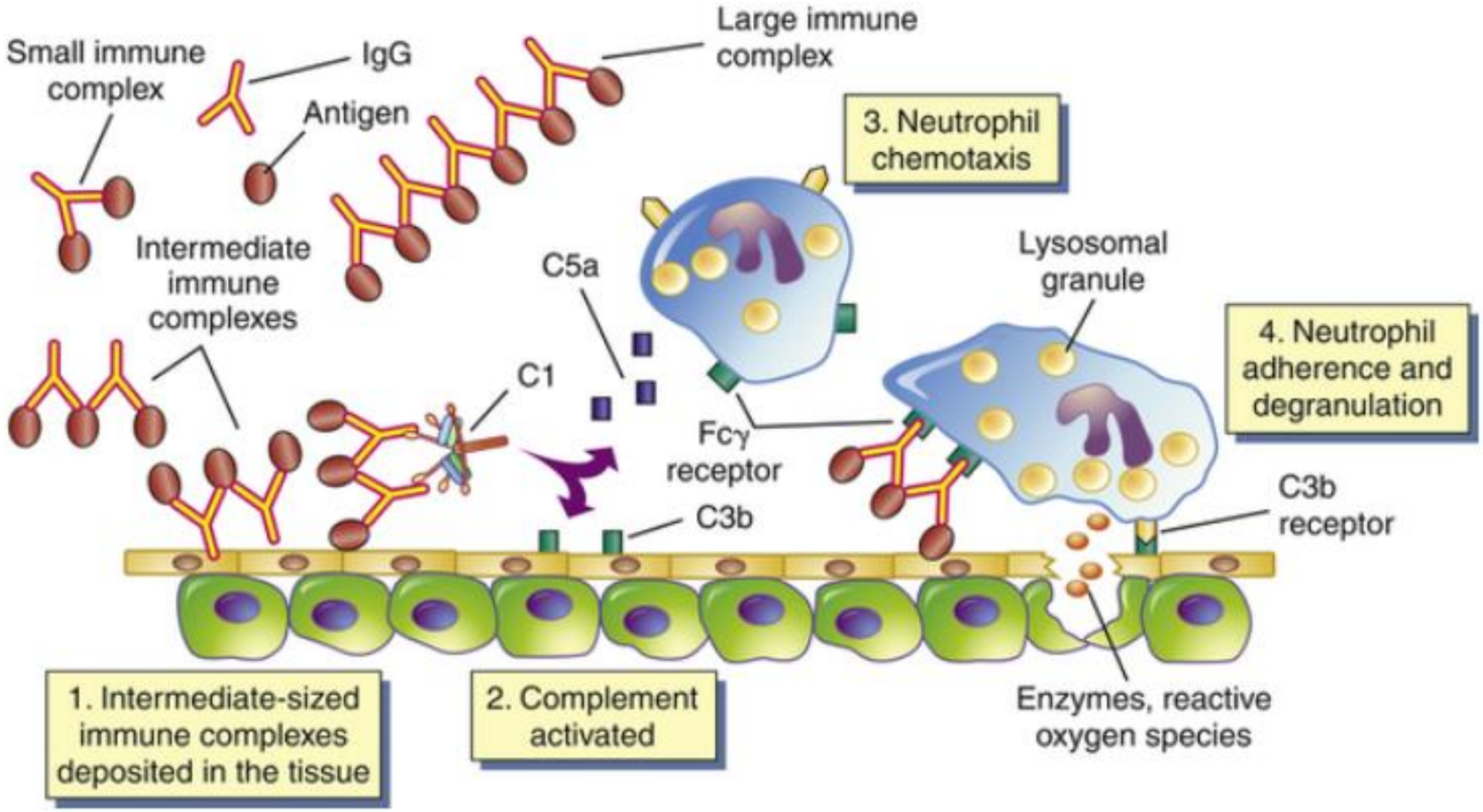
- If immune complexes are not removed from blood, they accumulate on wall of blood vessels and on tissue where filtration of blood and plasma occurs such as glomerular membrane, synovial membrane of joints etc.

- Type III hypersensitivity reaction is characterized by deposition of immune complexes on various tissues such as wall of blood vessels, glomerular basement membrane of kidney, synovial membrane of joints and choroid plexus of brain.

- Deposition of immune complexes initiates reaction resulting in damage of surrounding tissue and cause inflammation.


Basement membrane of blood vessel
1 Immune complexes are deposited in wall of blood vessel.
Ag
2 Presence of immune complexes activates complement and attracts inflammatory cells such as neutrophils.
Endothelial cell
Neutrophils
3 Enzymes released from neutrophils cause damage to endothelial cells of basement membrane.
© BENJAMIN/CUMMINGS

Mechanism of Type III hypersensitivity reaction:



Factors that causes deposition of immune complex and increase susceptibility to Type III hypersensitivity reaction:

1. Persistent infection:

-In persistent infection such as Malaria, large number of immune complexes are formed and deposited in tissues.

2. Complement deficiency:

-Complement removes immune complexes from blood, but when complement system is deficient, large amount of immune complexes circulates in blood and deposits in tissues.

3. Autoimmunity:

-In autoimmune disease, large amount of immune complexes are formed and deposited in tissues.

4. Genetic defects:

-In certain genetic defects, small and soluble immune complexes are formed that can not be phagocytosed

Examples

1. Localized Type III hypersensitivity reaction:

-Acute Arthus reaction

When antigen is injected or enters intradermally or subcutaneously, they bind with antibody to form localized immune complexes which mediate acute Arthus reaction within 4 to 8 hours.

2. Generalized Type III hypersensitivity reaction:

-Serum sickness.

When large amount of antigen enter blood stream and bind to antibody, circulating immune complexes formsThe manifestation of serum sickness depends on the quantity of immune complex as well as overall site of deposition. The site may vary but accumulation of complexes occurs at site of blood filtration.

-Generalized Type III hypersensitivity reaction at different site results in different diseases such as Glomerulonephritis (Kideny), vasculitis (arteries), Arthritis (synovial joints).

Delayed hypersensitivity reaction

- Delayed hypersensitivity reaction is mediated by sensitized CD4 T cells and manifests slowly usually after 24 hours or more.
- It is called delayed because symptoms appears days after exposure to antigen.
- In delayed hypersensitivity reaction, the effector molecules are various cytokines secreted by activated CD4 T cells themselves.
- Type-V hypersensitivity depends upon activation of T cells and occurs within cell mediated branch of immune response and termed as delayed type hypersensitivity reaction (DTH).

DTH occurs in 2 phases

- 1. Sensitization Phase

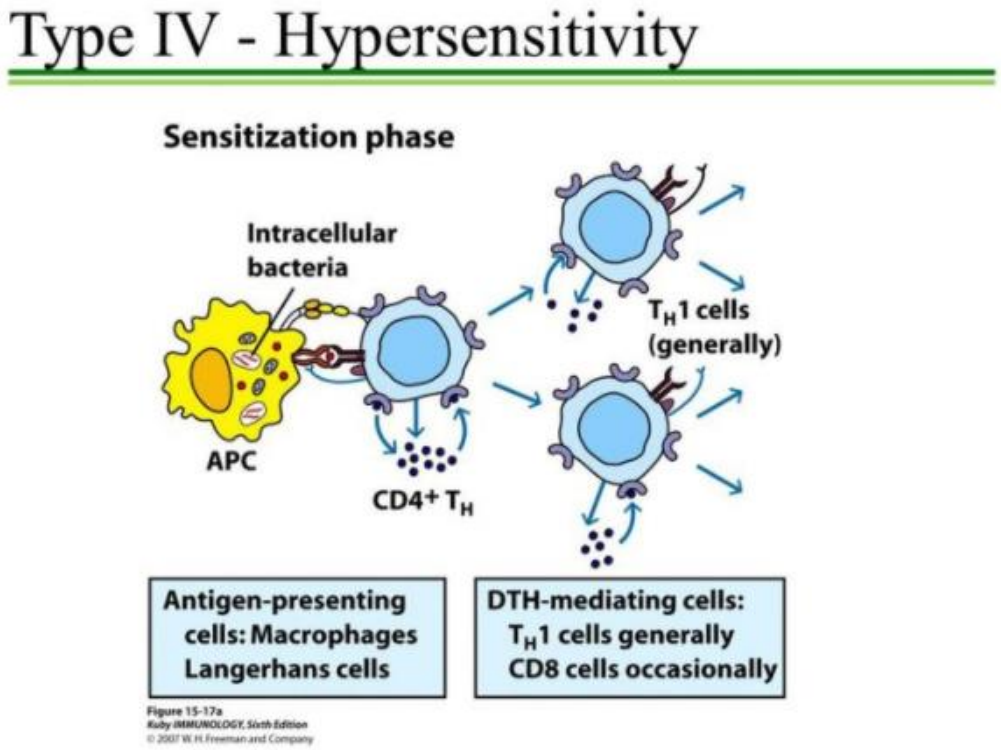


fig. sensitizing phase of Type IV – Hypersensitivity

- DTH begins with initial sensitization by primary contact with antigen. At first antigen is processed and presented by antigen presenting cells (APCs) to CD4+T cell.
- CD4 +T cells are activated to form TH cells.
- During this TH cells are clonally expanded by binding with MHC-II molecule carrying antigen by appropriate APCs. Varieties of APCs have been shown to be involved in activation of DTH response including langerhans cell and macrophages.
- CD4+ T cell are the primary cell activated during sensitizing phase of DTH response. However in some cases CD8 + cells are also found to induce DTH response.

- 2. Effector Phase

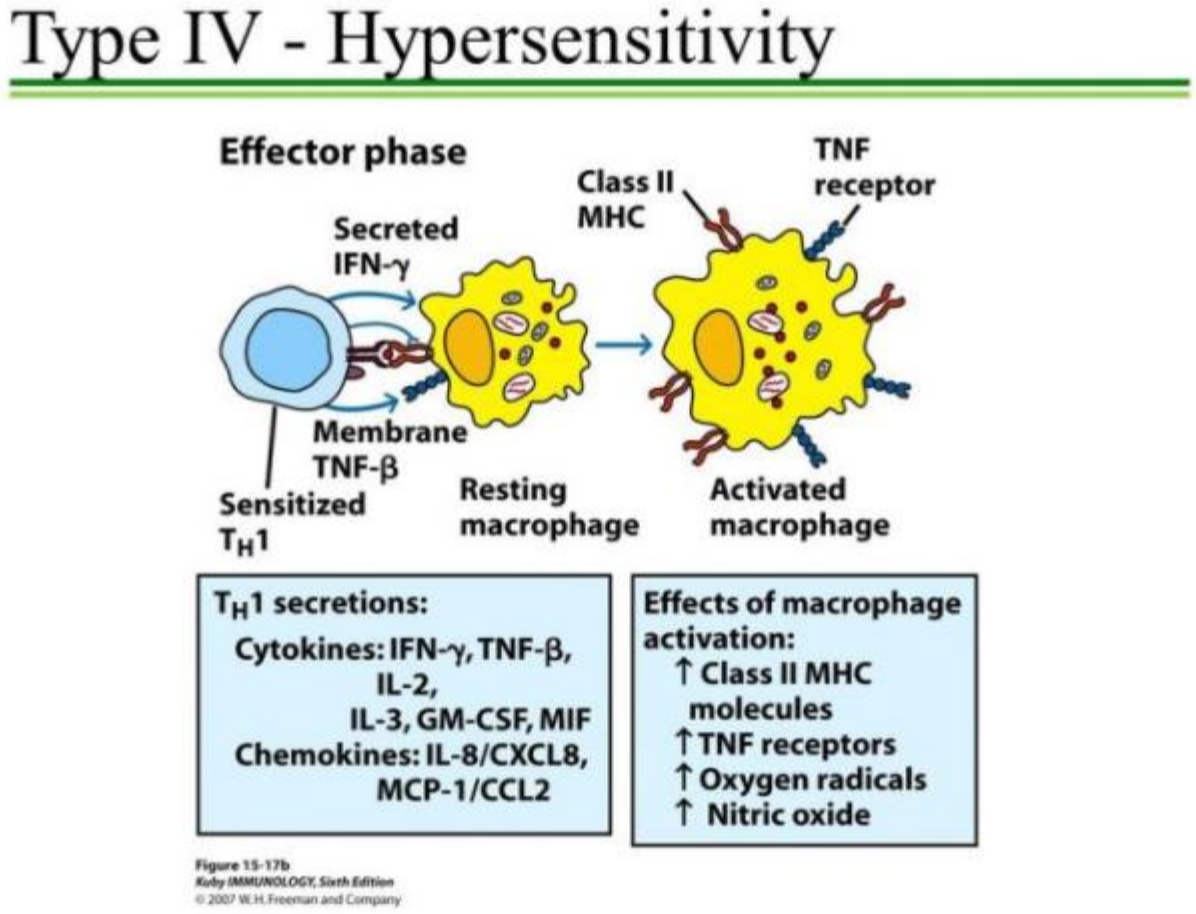


fig. effector pahse of Type IV – Hypersensitivity

- In this phase, TH1 cell secretes varieties of cytokines that recruits and activates macrophages and other non-specific inflammatory cells to the site of antigen injection.
- Macrophages are the principle effector of DTH response. The activated macrophages exhibit increased level of phagocytosis and increased ability to kill the antigen (microorganisms) by various cytotoxic lytic enzymes.
- Activated macrophages releases lytic enzymes that damage surrounding tissues and intracellular bacteria.
- The influx and activation of macrophages in DTH is important in host defense against intracellular bacteria and parasite, where circulating antibodies cannot reach them.
- concentration of lytic enzymes which destroy surrounding tissues leading to necrosis

- Increased phagocytic activity and build up lytic enzyme from macrophages in the area of infection leads to non-specific destruction of tissues and intracellular pathogens.
- Generally pathogens are killed rapidly with little tissue damage. However in some case, especially if the antigen is not easily cleared, a pro-long DTH response can itself become destructive to host as intensive and chronic inflammation develops into a visible granulomatous reaction.
- A granuloma develops when continuous activation of macrophages induces the epitheloid shape and some time fusion of macrophages to form multinucleated giant cells. These giant cells displace normal cells forming palpable nodules and release high

Examples

- Tuberculin skin test (Mantoux test)
- Lepromin test
- Brucellergin test

Diagnosis of hypersensitivity

- Diagnosis of type I hypersensitivities is a complex process requiring several diagnostic tests in addition to a well-documented patient history.
- Serum IgE levels can be measured, but elevated IgE alone does not confirm allergic disease.
- Testing through a prick puncture skin test (PPST) or an intradermal test can be performed.
- PPST is carried out with the introduction of allergens in a series of superficial skin pricks on the patient's back or arms . PPSTs are considered to be the most convenient and least expensive way to diagnose allergies

- The intradermal test: requires injection into the dermis with a small needle. This needle is attached to a syringe containing a small amount of allergen.

- Both the PPST and the intradermal tests are observed for 15–20 minutes for a wheal-flare reaction to the allergens. Measurement of any wheal (a raised, itchy bump) and flare (redness) within minutes indicates a type I hypersensitivity, and the larger the wheal-flare reaction, the greater the patient's sensitivity to the allergen.

- Type III hypersensitivities can often be misdiagnosed because of their nonspecific inflammatory nature. The symptoms are easily visible, but they may be associated with any of a number of other diseases.

- A strong, comprehensive patient history is crucial to proper and accurate diagnosis. Tests used to establish the diagnosis of hypersensitivity pneumonitis (resulting from type III hypersensitivity) include bronchoalveolar lavage (BAL), pulmonary function tests, and high-resolution computed tomography (HRCT).

Treatment

- Prevention of allergic reactions can be achieved by **desensitization** (hyposensitization) therapy, which can be used to reduce the hypersensitivity reaction through repeated injections of allergens.

- Extremely dilute concentrations of known allergens (determined from the allergen tests) are injected into the patient at prescribed intervals (e.g., weekly). The quantity of allergen delivered by the shots is slowly increased over a buildup period until an effective dose is determined and that dose is maintained for the duration of treatment, which can last years.

- Emergency systemic anaphylaxis is treated initially with an epinephrine injection, which can counteract the drop in blood pressure. Follow-up treatment generally involves giving the patient antihistamines and slow-acting corticosteroids for several days after the reaction to prevent potential late-phase reactions.
- anti-inflammatory drugs.
- Treatment of type IV hypersensitivities includes antihistamines, anti-inflammatory drugs, analgesics, and, if possible, eliminating further exposure to the antigen.

Thank You

BCHEM 471
Autoimmunity

Amma Larbi(PhD)

What is Autoimmunity

- Autoimmune is a disorder of the body's defense mechanism in which an immune response is generated against component or products of its own tissues treating them as foreign material and attacking them.

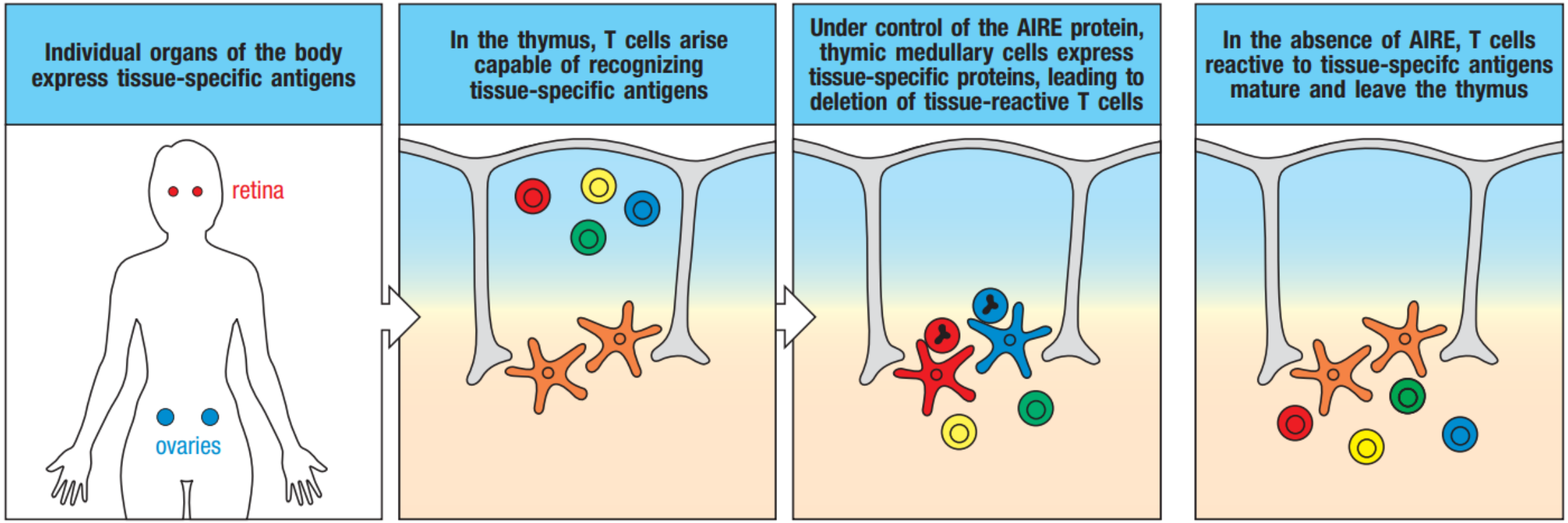
- It refers to ways in which loss of self-tolerance can generate self-reactive lymphocytes that cause tissue damage.

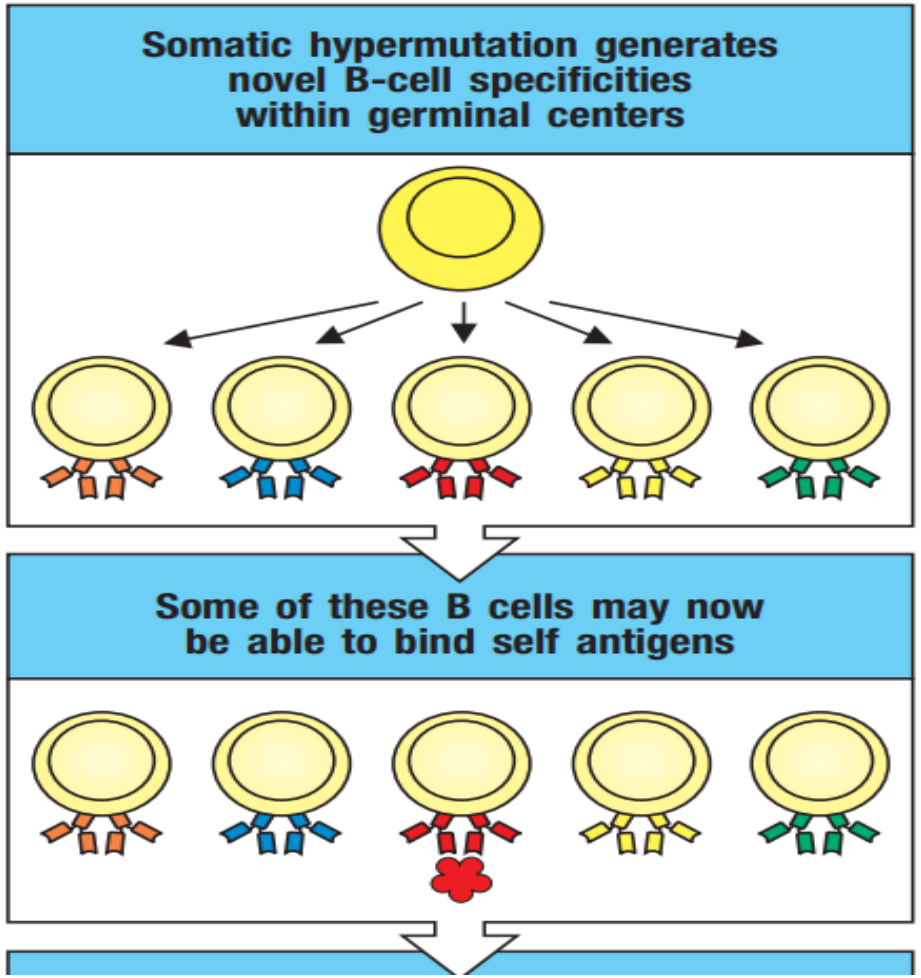
- The disorder caused by inflammation and destruction of tissues by the body's immune response as a result of autoimmunity is known as autoimmune disease.

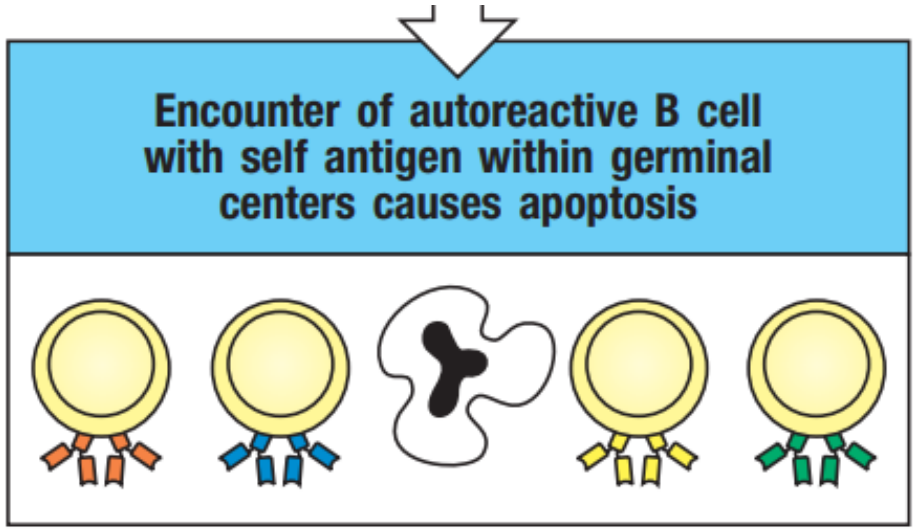
Self Tolerance

Layers of self-tolerance		
Type of tolerance	**Mechanism**	**Site of action**
Central tolerance	Deletion Editing	Thymus (T cells) Bone marrow (B cells)
Antigen segregation	Physical barrier to self-antigen access to lymphoid system	Peripheral organs (e.g., thyroid, pancreas)
Peripheral anergy	Cellular inactivation by weak signaling without co-stimulus	Secondary lymphoid tissue
Regulatory T cells	Suppression by cytokines, intercellular signals	Secondary lymphoid tissue and sites of inflammation; multiple tissues in steady state
Functional deviation	Differentiation of regulatory T cells that limit inflammatory cytokine secretion	Secondary lymphoid tissue and sites of inflammation
Activation-induced cell death	Apoptosis	Secondary lymphoid tissue and sites of inflammation

The making and breaking of Self Tolerance




Somatic hypermutation generates novel B-cell specificities within germinal centers
Some of these B cells may now be able to bind self antigens


Encounter of autoreactive B cell with self antigen within germinal centers causes apoptosis

Proposed mechanism for induction of autoimmunity

- A variety of mechanisms have been proposed to account for the T-cell mediated generation of autoimmune disease. And it is likely that autoimmune disease does not develop from a single event rather from a number of different events. These include:
- Forbidden clone
- Altered antigen
- Sequestered antigen
- Immunological deficiency theory
- Genetic influence

❖Forbidden clone

- Mutation in the lymphocytes may result in the formation of changed or altered clone. These altered clone may recognize host as foreign and lead to development of autoimmunity.

❖Altered antigen

- Some of the antigen on the host cell get altered by chemical, biological or physical means. Thus formed new antigenic determinants which may be recognized as foreign by the host.

❖Sequestered antigen

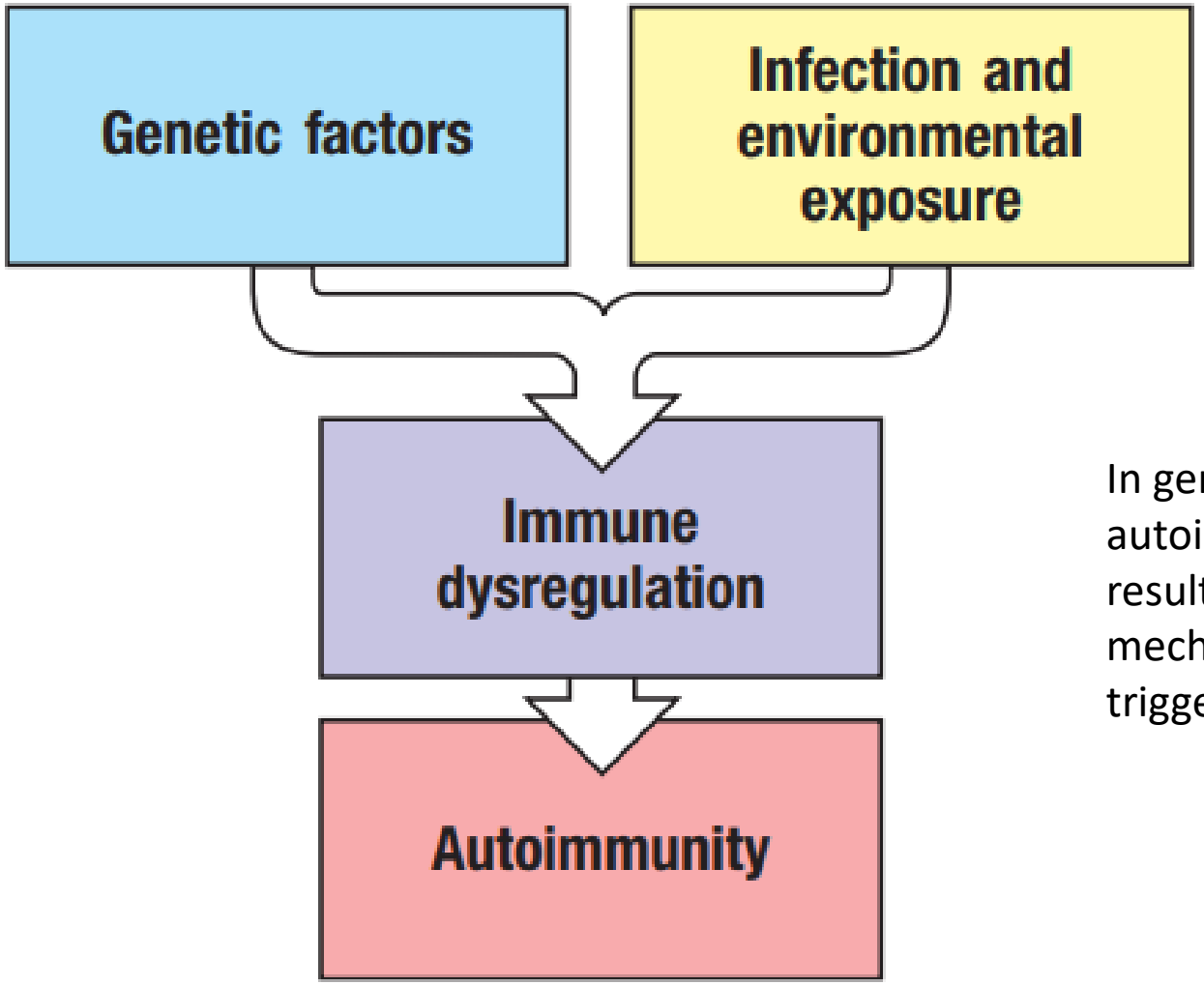
- Some of the antigen in the body are hidden from cells of immune system.
- If the organs containing such antigen are damaged, it causes exposure of sequestered antigen thus an immune reaction to these antigen may occur.

❖ Immunological deficiency theory

- According to this theory, mutation or loss of immune regulatory power. i.e. deficiency in immune system results in a condition in which self-antigen behaves as foreign.

❖Genetic influence

- This was determined by family studies. It is well recognized that certain immune disorder predominate in females and families.
- This has strongly supported the role of genetic influence in autoimmunity.
- Genetic links have occurred between disease and HLA antigens.



In genetically predisposed individuals, autoimmunity may be triggered as a result of the failure of intrinsic tolerance mechanisms and/or environmental triggers such as infection

Types of autoimmune disease:

- On the basis of pathogenic mechanism, autoimmune disease are classified into two types:

- **Organ specific autoimmune disease**
- **Systematic autoimmune disease**

1. Organ specific autoimmune disease

- This autoimmune disease is directed against a component of one particular type of organ.

- The organ specific autoimmune disease can further be divided into two groups:

- Autoimmune disease mediated by direct cellular damage

- Autoimmune disease mediated by stimulating or blocking auto antibodies:

Autoimmune disease mediated by direct cellular damage

- This type of damage occur when lymphocytes or antibodies bind to cell membrane antigens, causing cellular lysis or inflammatory response in affected organ.

- The damaged cellular structure is then replaced by connective tissue (fibrous) & it losses its function.

- **Examples**: Hasimoto's thyroiditis, autoimmune anaemia, Good pasteur's syndrome, Insulin dependent diabetes mellitus.

Hashimoto's Thyroiditis

- In Hashimoto thyroiditis, an individual produces antibodies & sensitized TH1 Cell specific for thyroid antigens.
- An attending delayed type hypersensitivity (DTH) response is characterized by an intense infiltration of the thyroid gland by lymphocytes, macrophages and plasma cells which form lymphocytic follicles and germinal centers.
- The ensuring inflammatory response cause goiter or visible enlargement of the thyroid gland, a physiological response to hypothyroidism.

- Hypothyroidsm is caused when antibodies are formed to a number of thyroid proteins including thyroglobulin and thyroid peroxidase, both of which are involved in the uptake of iodine.
- Binding of auto-antibodies to these protein interfere with thyroid gland functioning.

Goodpasture's Syndrome

- In Goodpasture's syndrome, auto-autobodies specific for certain basement membrane antigen bind to basement membrane of kidney glomeruli and alveoli of lungs.
- Subsequent complement activation leads to direct cellular damage and an ensuring inflammatory response meditated by a buildup of complement split products.
- Damage to the glomerulus and alveolar basement membrane leads to progressive kidney damage and pulmonary hemorrhage.
- Death may ensure within several month of the onset of symptoms

Autoimmune anemias

- Autoimmune anemias include pernicious anemia, autoimmune hemolytic anemia (AIHA) and drug induced hemolytic anemia.
- **Pernicious anemia** is caused by auto- antibodies to intrinsic factor, a membrane bound intestinal protein on gastric parietal cells which facilitate uptake of vitamin B12 from small intestine. Binding of auto-antibody to intrinsic factor block absorption of vitamin B12. In absence of sufficient vitamin B12, which is necessary for proper hematopoiesis, the number of functional mature RBC decrease below normal.

- **Autoimmune hemolytic anemia:** An individual with autoimmune hemolytic anemia makes auto-antibody to Red-blood cell antigen, triggering complement mediated lysis or antibody-mediated opsonization & phagocytosis of RBC.
- **In drug induced hemolytic anemia,** certain drugs such as penicillin or anti-hypertensive agents like methyldopa interact with RBC, the cells become antigenic.

Insulin Dependent Diabetes mellitus (IDDM)

- IDDM is caused by an autoimmune attack on pancreas.
- The attack is directed against specialized insulin producing beta-cell that are location in spherical cluster islets of Langerhans, scattered throughout the pancreas.
- The autoimmune attack destroys beta cell resulting in decreased production of insulin and consequently increased level of blood glucose.
- Several factors are important in destruction of beta cells, first activated CTLs migrate into an islet and begin to attack the insulin producing cells.

- The CTL infiltration & activation of macrophages, frequently referred to as insulitis which is followed by cytokine release and presence of auto antibodies which leads to a cell mediated DTH.

- The auto-antibodies to beta cells may contribute to cell distribution by facilitating either antibody-mediated complement lysis or antibody-dependent cell-mediated cytotoxicity (ADCC).

Autoimmune disease mediated by stimulating or blocking auto antibodies

- In some cases, antibodies act as antagonist & bind to hormone receptor stimulating inappropriate activity. This usually leads to overproduction of mediators or increase cell growth.
- They also bind to hormone receptor function and thereby block receptor function. This causes impaired secretion of mediators and gradual atrophy of the affected organ.
- **Examples**: Grave's disease, Myasthenia gravis.

Grave's disease

- The production of thyroid hormones is carefully regulated by thyroid stimulating hormone (TSH) produced by pituitary gland. The binding of TSH to receptor on thyroid cell activates adenylate cyclase enzyme stimulating synthesis of thyroxine and tri-iodo thyroxine.
- A patient with Graves' disease produces autoantibody (LATS) that bind to receptor of TSH & mimic the normal action of TSH, activating adenylate cyclase & resulting in production of thyroid hormones. Unlike TSH, however autoantibody are not regulated and consequently they overstimulate the thyroid gland.

Myasthenia gravis

- It is an autoimmune disease mediated by blocking antibodies.

- A patient with this disease produces auto antibodies that bind the acetylcholine receptor on motor end plates of muscles, blocking the normal binding of acetyl choline. The result is progressive weakening the skeletal muscles.

- It also inducing complement mediated lysis of cells and the antibodies cause the destruction of the cells bearing receptors.

2. Systematic autoimmune disease

- It is the type of autoimmune disease which is directed against an antigen that is present in many different sites and can include involvement of several organs and tissues.

- These disease reflect a general defect in immune regulation that result in hyperactive T-cells and B-cells.

- **Examples**: Rheumatoid arthritis, Systematic lupus erythematosus (SLE), multiple sclerosis.

Systemic Lupus erythematosus

- One of the best example of a systemic autoimmune disease is systemic lupus erythematosus (SLE).
- The individual affected by SLE may produce auto-antibodies to a vast array of tissues, antigens, such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors.
- Interaction of these auto-antibodies with their specific antigens produces various symptoms.

- Auto antibody specific for RBC and platelets for examples, can lead to complement mediated lysis resulting in hemolytic anemia and thrombocytopenia, respectively.

- When immune complex of auto antibodies with various nuclear antigens are deposited along the walls of small blood vessels, a type III hypersensitivity reaction develops.

- The complexes activates the complement system and generate membrane- attack complexes and complement split produces that damage the wall of the blood vessel, resulting in vasculitis and glomerulonephritis.

Multiple sclerosis (MS)

- It is the most common cause of neurologic disability associated with autoimmune disease.
- With this disease, production of auto-reactive T-cell that participate in the formation of inflammatory lesions along the myelin sheath of nerve fibers.
- The cerebrospinal fluid of patient with active MS contains activated T lymphocytes, which infiltrate the brain tissue and cause characteristic inflammatory lesions, destroying the myelin.
- Since myelin function to insulate the nerve fibers, a breakdown in the myelin sheath leads to numerous neurologic dysfunctions.

Rheumatoid arthritis

- Rheumatoid arthritis is common autoimmune disorder.
- Many individuals with rheumatoid arthritis produce a group of auto-antibodies called rheumatoid factors that are reactive with determinants of Fc region of IgG antibody.
- The classic rheumatoid factor is an IgM antibody with that reactivity. Such auto-antibodies bind to normal circulating IgG, forming IgM – IgG complexes that are deposited in the joints.
- The immune complexes can activate the complement cascade, resulting in type III hypersensitive reaction which leads to chronic inflammation of the joints.

Autoimmune diseases involve all aspects of the immune response			
Disease	**T cells**	**B cells**	**Antibody**
Systemic lupus erythematosus	Pathogenic Help for antibody	Present antigen to T cells	Pathogenic
Type 1 diabetes	Pathogenic	Present antigen to T cells	Present, but role unclear
Myasthenia gravis	Help for antibody	Antibody secretion	Pathogenic
Multiple sclerosis	Pathogenic	Present antigen to T cells	Present, but role unclear

Diagnosis

- No single test can diagnose most autoimmune diseases. Diagnosis is based on a combination of tests and a review of symptoms and physical examination.
- The antinuclear antibody test (ANA) is often one of the first tests that doctors use when symptoms suggest an autoimmune disease. A positive test means you may have one of these diseases, but it won't confirm exactly which one you have or if you have one for sure.

- C Reactive Protein

- Autoantibody titers (anti DNA, anti phospholipids, etc)
- Presence of Rheumatoid Factor
- Erythrocyte sedimentation rate
- Neurological exam – MS
- Fasting glucose – Diabetes

Treatment

- Treatments can't cure autoimmune diseases, but they can control the overactive immune response and bring down inflammation or at least reduce pain and inflammation. Drugs used to treat these conditions include:

-nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen (Motrin, Advil) and naproxen (Naprosyn)

-immune-suppressing drugs :The three cytotoxic drugs most commonly used as immunosuppressants are azathioprine, cyclophosphamide, and mycophenolate. Others include prednisone, cyclosporin A.

Thank you