Cihan University/ Sulaimaniya

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 5: Infection

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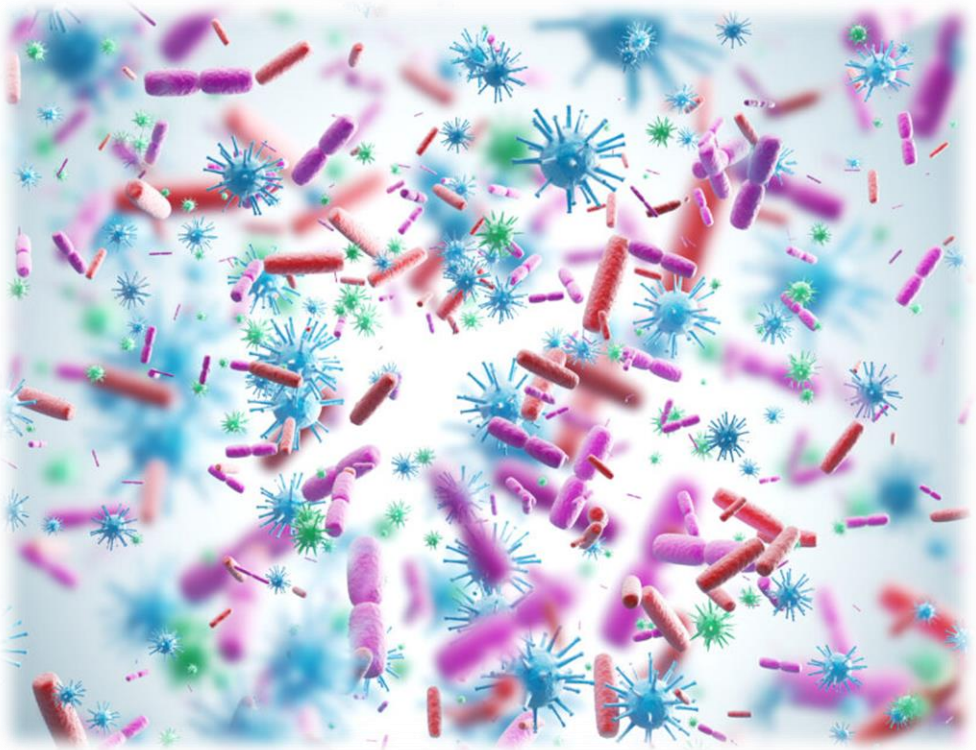
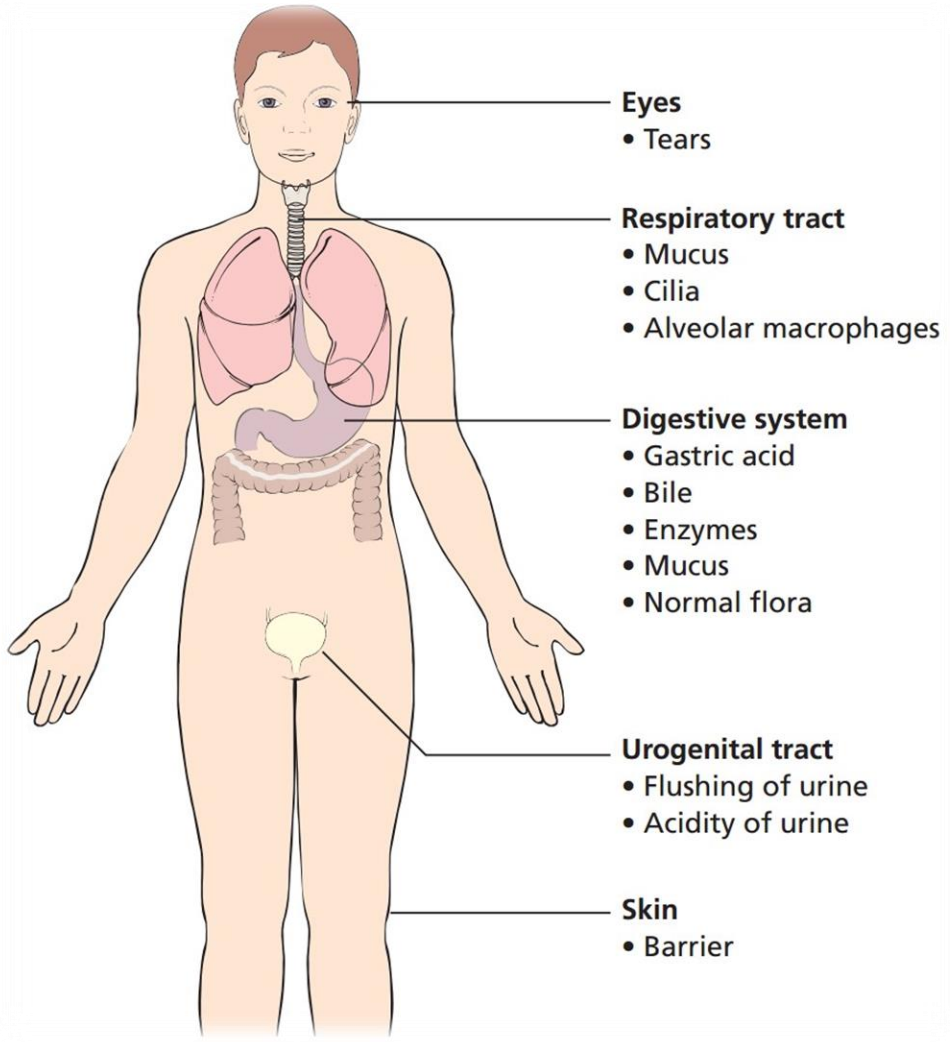
Introduction

- Infectious disease is the major cause of morbidity and mortality worldwide.
- In Africa alone, the World Health Organization estimates that about 100 million people suffer from malaria.
- New infections, such as Helicobacter pylori (recognized in 1989),
- New variant Creutzfeldt–Jakob disease (the causative prion was discovered around the same time),
- The epidemic of severe acute respiratory syndrome (SARS).
- Antibiotic resistance and the increased spread of *Clostridium diffcile* in hospitals.



Factors Influencing the Extent and Severity of an Infection

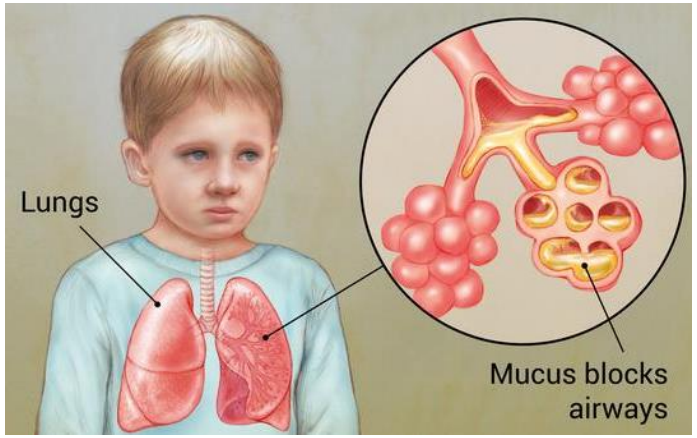
- Pathogen factors:
  - Dose (i.e. degree of exposure)
  - Virulence of organism
  - Route of entry
- Host factors:
  - Integrity of non-specifc defences
  - Competence of the immune system
  - Genetic capacity to respond effectively to a specifc
- Organism:
  - Evidence of previous exposure (natural or acquired)
  - Existence of co-infection

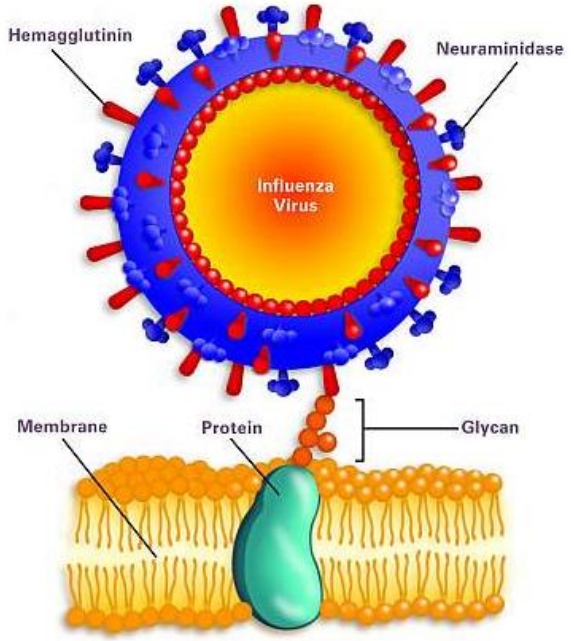


Normal Resistance To Infection

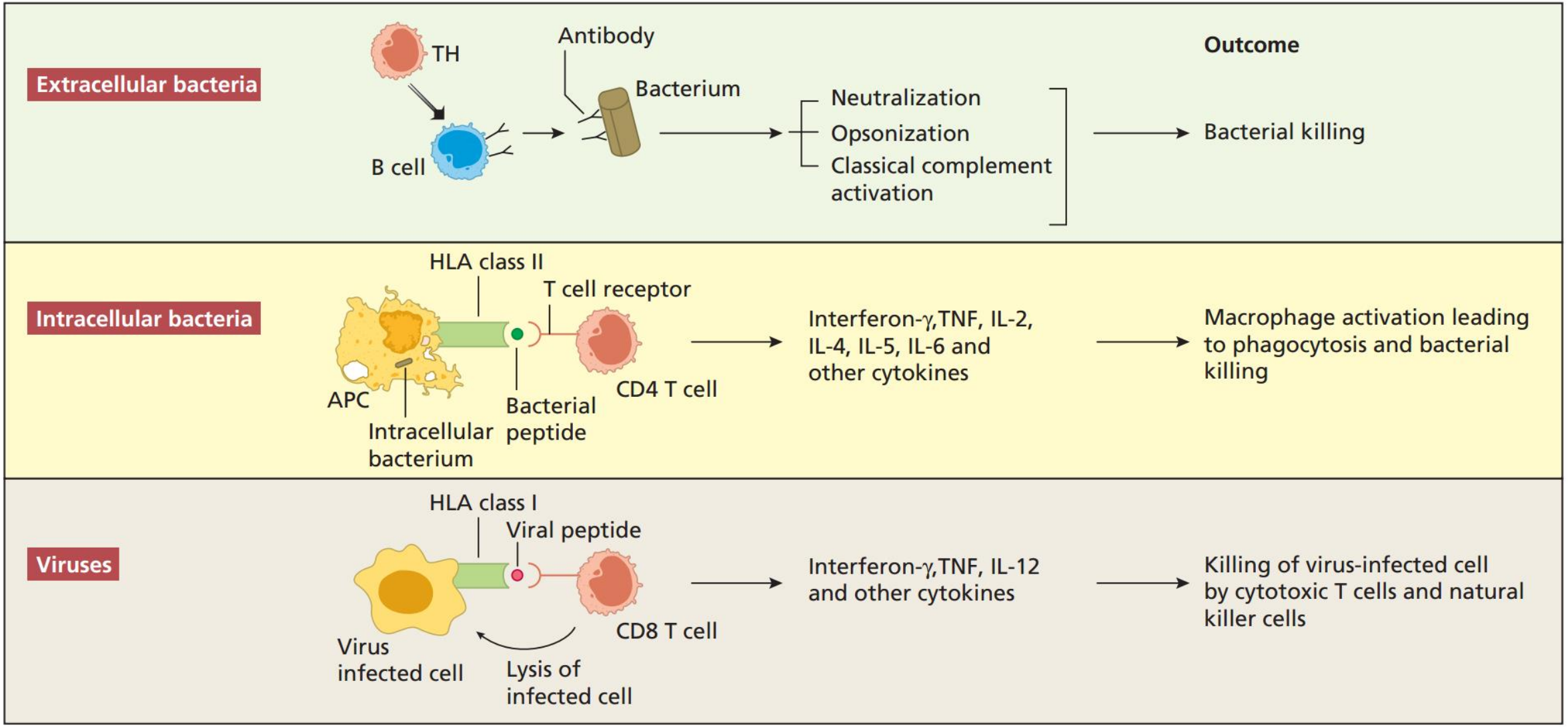
A- Non-specific or Natural Resistance:

- Non-specific or natural resistance refers to barriers, secretions and the normal flora that make up the external defenses, together with the actions of phagocytes and complement.
- Mechanical barriers are highly effective, and their failure often results in infection; for example, defects in the mucociliary lining of the respiratory tract (as in **Cystic fibrosis** is an inherited condition that causes sticky mucus to build up in the lungs and digestive system.)
- However, many common respiratory pathogens have evolved specific substances on their surfaces (e.g. the **haemagglutinin of influenza virus**), which help them attach to epithelial cells and so breach physical barriers.





B- Specific Immune Responses To Microorganisms:



Viral infection

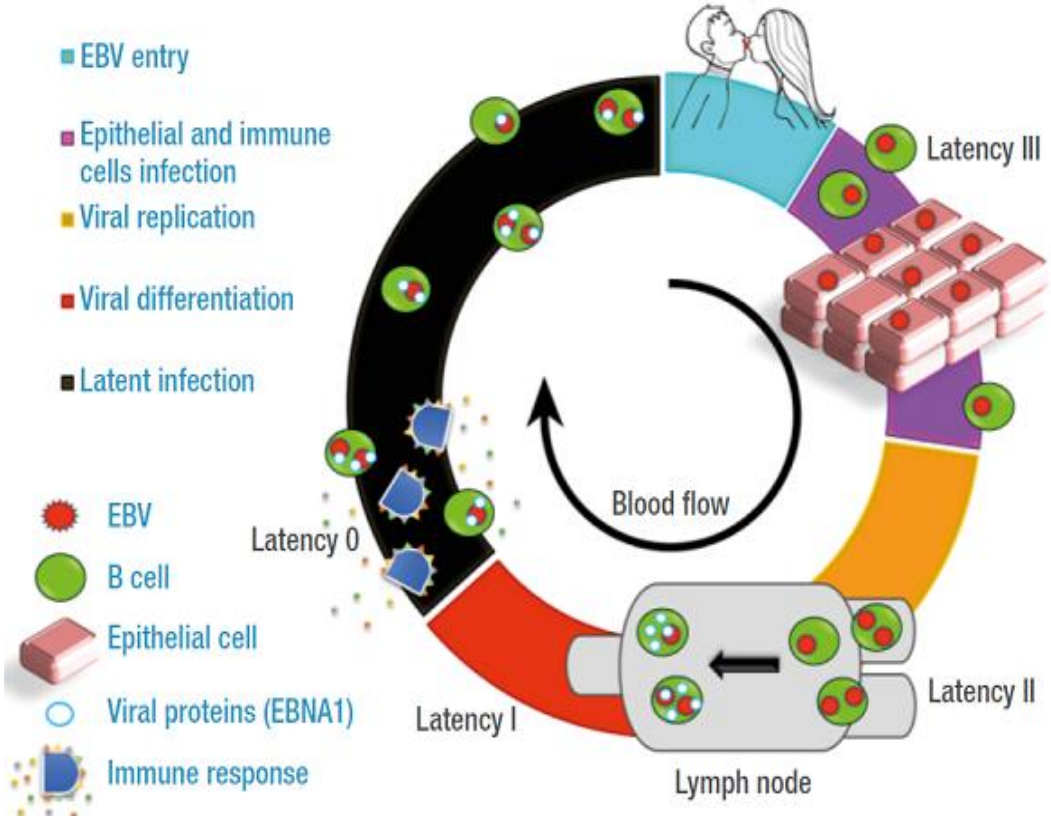
Epstein–Barr virus infection:

- Infectious mononucleosis is caused by the Epstein–Barr virus (EBV), a member of the herpes group of viruses. By the age of 3 years, 99% of children in developing countries have been infected sub-clinically with EBV.
- In developed countries, clinically recognizable infection most frequently occurs in the15–25-year age group.
- The virus is excreted in oropharyngeal secretions for some months, and is responsible for person-to person transmission.
- The pattern of antibody responses to different EBV antigens helps to distinguish acute or subclinical infection from past EBV infection.
- Antibodies to EB nuclear antigen (EBNA) develop about 4 months after infection and remain for life.

Epstein–Barr virus infection: Life Cycle

- EBV produces disease by infecting and transforming B lymphocytes via the CD21 molecule on the B-cell surface.
- Infected B cells proliferate like tumour cells, and small numbers may produce free virus which can then transform other B lymphocytes.
- Primary EBV infection is stopped by **two defenses**:

1. T-cell immune response predominantly (CD8+ cytotoxic T lymphocytes) capable of eliminating almost all virus-infected cells, and
2. Virus-neutralizing antibodies which prevent the spread of infection from one target cell to another.

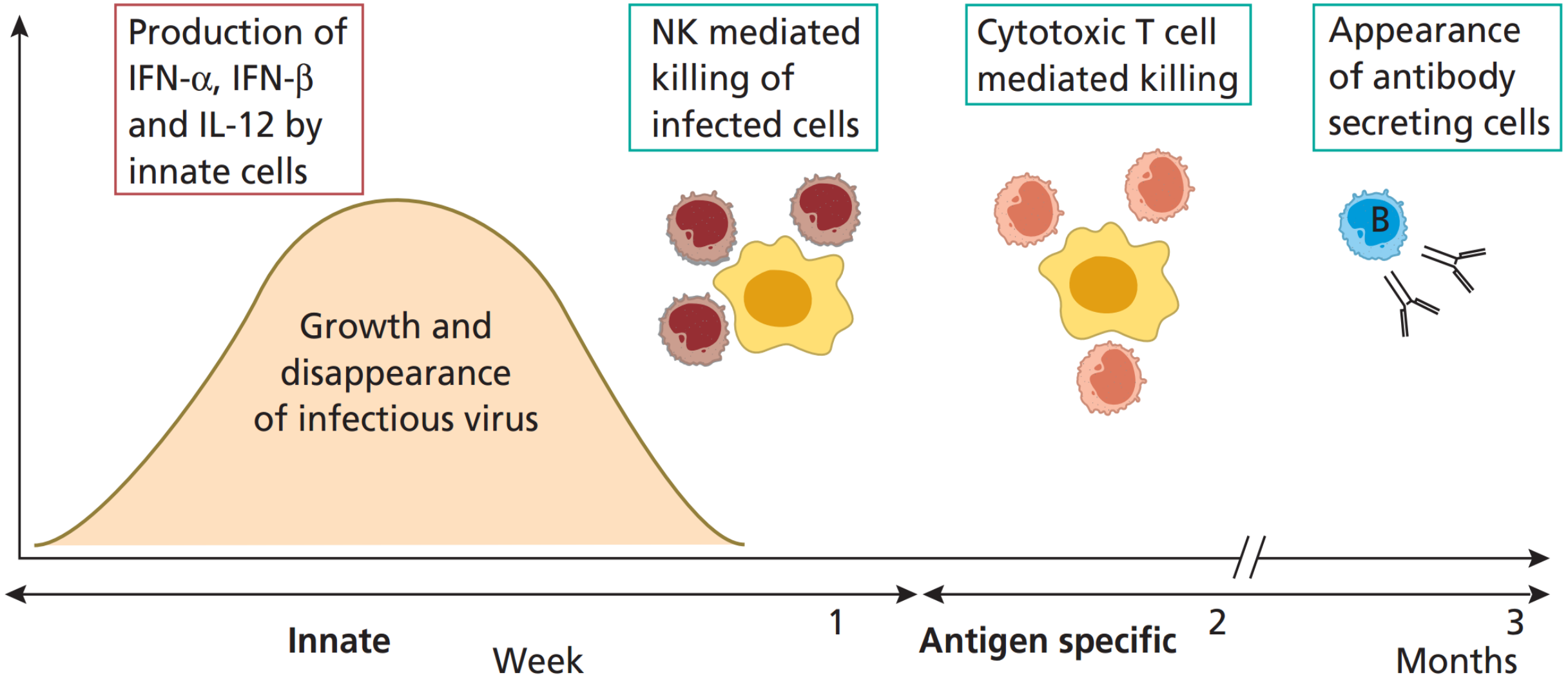


Viral infection

Herpes Viruses:

- The herpes virus group consists of at least 60 viruses, eight of which commonly infect humans.
- Two features of pathogenesis are common to all human herpes viruses.
  1. First, close physical contact must occur between infected and uninfected human individuals for transmission of virus and no other species is involved.
  2. Second, after a primary infection, herpes viruses persist in the host throughout life.
- Immunological reactions are thus of two kinds: those directed against the virion and those that act upon the virus-infected cell.
- In general, immune responses to the virion are predominantly humoral, while T-cell-mediated responses act on virus-infected cells.

Time Sequence of Immune Response To Viral Infection



Viral Strategies To Evade The Immune Response

evasion strategy	Possible mechanisms	Examples
RNAi	Encodes suppressors for RNA silencing (SRS) to inhibit RNAi responses	Ebolavirus
Inhibition of TAP, Tapasin and disruption of MHC-I	Post-translational strategies inhibiting peptide transport and MHC-I biosynthesis by blocking peptide transporter (TAP) and chaperones like tapasin	HCMV
	Viral proteins, BNLF2a and mK3 inhibit TAP associated MHC-I response by targeting host tail-anchored protein integration machinery and regulating ubiquitination of TAP/tapasin, respectively.	EBV, HSV-1, BHV-1,GHV
	Viral proteins like UL49.5 and US6 alter the conformation, degrade the TAP1/2 interfere with ATP binding. HSV ICP47 protein interferes with peptide binding.	PRV, HCMV HSV
LANA1 mediated evasion	Inhibits the presentation of Major Histocompatibility complex class I (MHC-I)	KSHV, EBV
IRF3 production	Inhibits IFN-γ and CIITA and thus MHC-I expression.	KSHV
Nef proteins	Nef proteins down-regulate MHC-I presentation of viral peptides.	SIV, HIV
Viral NLR homolog	Homolog inhibits the inflammasome and also block caspase-1 activation, IL-1β and IL-18 processing	KSHV
	Impairs RIG-I-like receptor-dependent signaling inhibiting IFN and TNF-α.	HCV
Encoding VP35 proteins PRR control	TLRs and RLRs are taken into virus control of PRR signaling and regulation of immune programs	EBV
Inactivating MDA5	MDA5 is a cytosolic PRR that is inactivated.	Paramyxovirus
NF-κB suppression	Prevents NF-κB dependent gene expression by retaining p65 in cytoplasm when V protein binds to p65 (RelA)	Measles virus
Proteases targeting signal transduction	Block IFN induction by affecting molecules of the innate immune pathways	HAV, HCV
Degradation of cellular TRIF	Replication and transcription activator (RTA) degrades TRIF	KSHV
CD1d down regulation	Viral protein E5 targets CD1d (a sentinel molecule bridging innate and adaptive immunity) by inhibiting calnexin-related CD1d trafficking	HPV

Bacterial infection

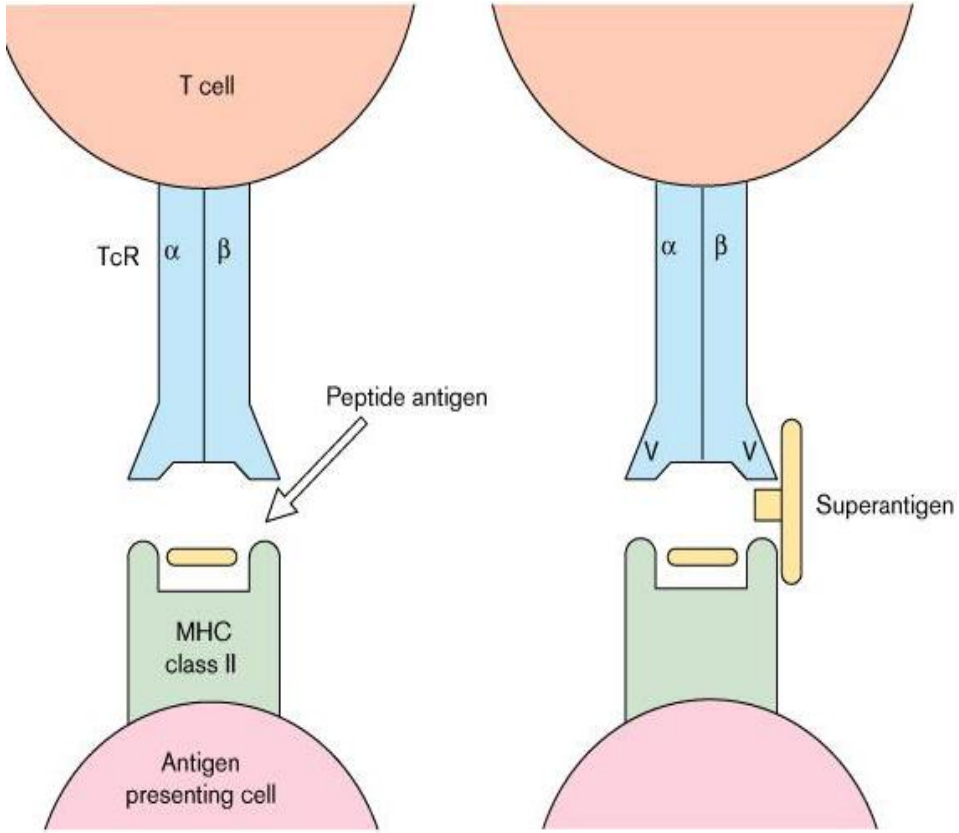
Normal immune responses to bacterial infections:

- There are two major categories of bacterial antigens that provoke immune responses:
- Soluble (diffusible) products of the cell (e.g. toxins),
- Structural antigens that are part of the bacterial cell (such as LPS).
- Many bacterial antigens contain lipid in association with cell-wall glycoproteins; the presence of lipid appears to potentiate the immunogenicity of associated antigens.
- Most bacterial antigens are T-cell dependent, requiring helper T lymphocytes for the initiation of humoral and cell-mediated immunity.
- However, some bacterial antigens, particularly capsule polysaccharides, are relatively T independent: these are characterized by their high molecular weight and multiple, repeating antigenic determinants.
- In children, adequate antibody responses to these antigens can take 2–4 (sometimes even 6) years to develop.

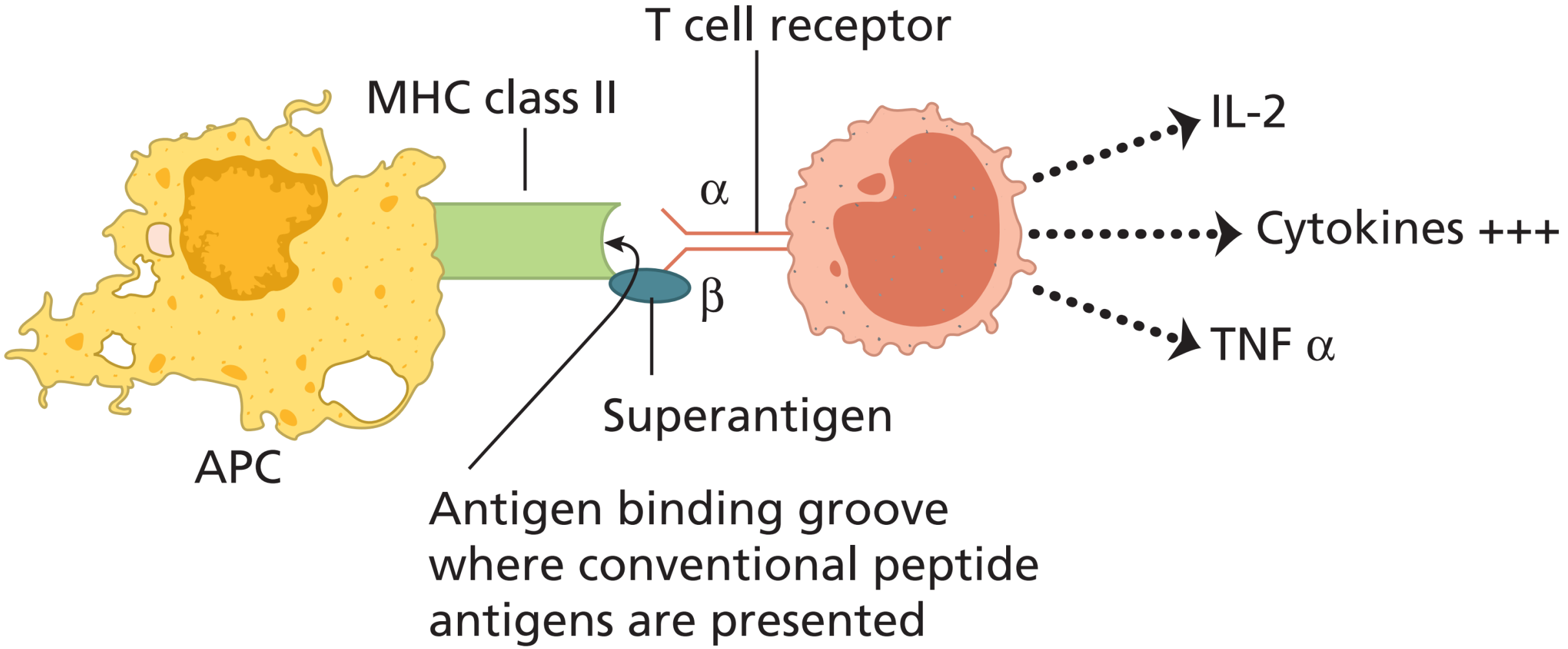
Bacterial Infection

Bacteria as superantigens:

- Some streptococcal toxins are potent activators of T cells by virtue of their ability to act as superantigens.
- T-cell activation with selective usage of certain T-cell receptor Vβ genes is a feature of superantigen-associated diseases. Consequently, these disorders are characterized by:
  - Marked cytokine release,
  - High fever,
  - Hypotension,
  - Multisystem involvement.
- Superantigen-associated diseases:
  - ❖Toxic shock syndrome:
    - Streptococcal
    - Staphylococcal
    - Clostridial (Clostridium perfringens)
    - Yersinial (Yersinia enterocolitica)
  - ❖Kawasaki disease:
    - No organism yet identified (superantigen association based on cytokine profile)



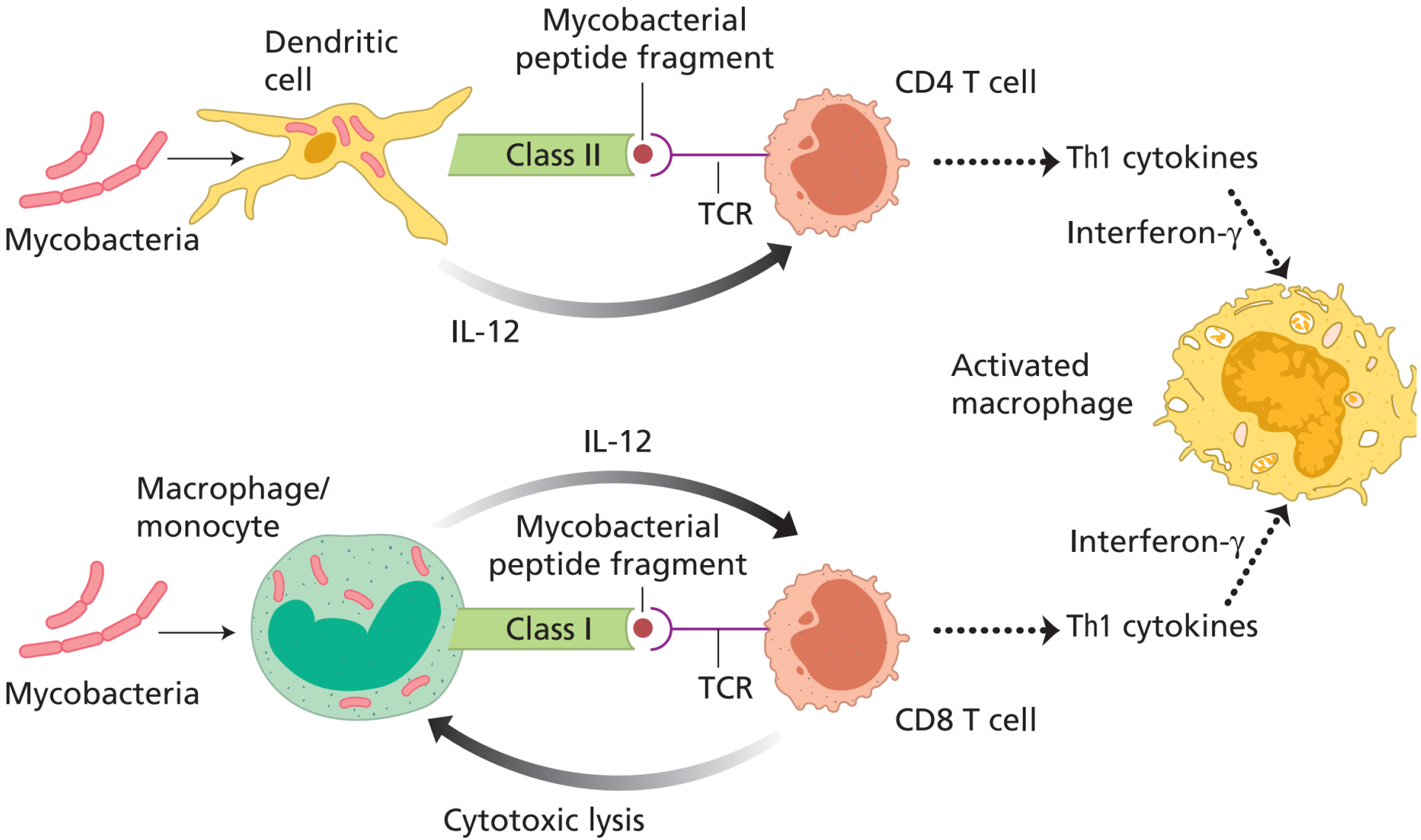
Superantigen-induced T-cell Stimulation



Bacterial Evasion of Immune Defenses

Infection process	Host defense	Bacterial evasion mechanisms
Attachment to host cells	Blockage of attachment by secretory IgA antibodies	Secretion of proteases that cleave secretory IgA dimers (*Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae*) Antigenic variation in attachment structures (pili of *N. gonorrhoeae*)
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells Mechanisms for surviving within phagocytic cells Induction of apoptosis in macrophages (*Shigella flexneri*)
	Complement-mediated lysis and localized inflammatory response	Generalized resistance of gram-positive bacteria to complement-mediated lysis Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria)
Invasion of host tissues	Ab-mediated agglutination	Secretion of elastase that inactivates C3a and C5a (*Pseudomonas*)
Toxin-induced damage to host cells	Neutralization of toxin by antibody	Secretion of hyaluronidase, which enhances bacterial invasiveness

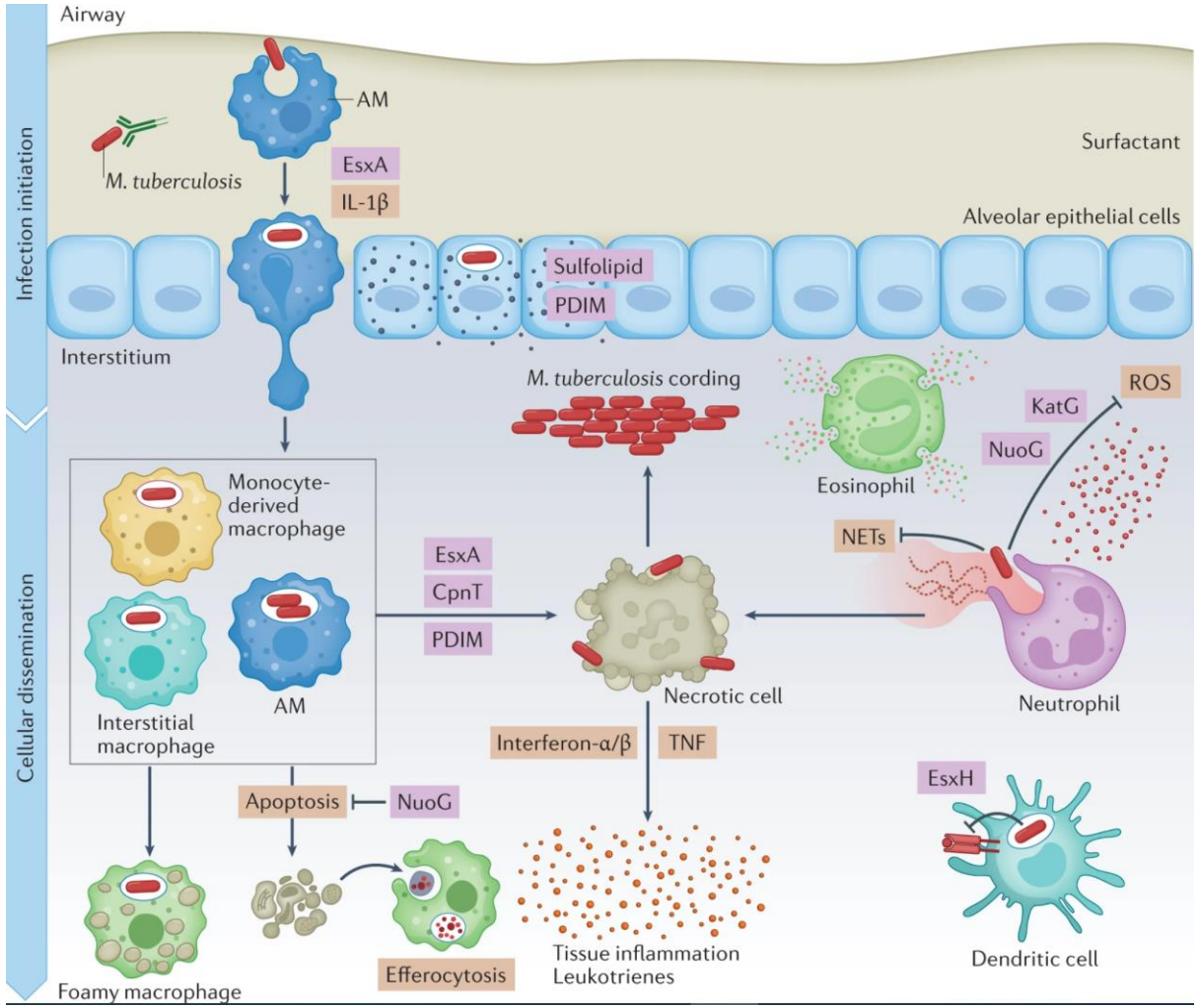
Role of Immune Response To Mycobacteria



Mycobacterial Evasion of the Immune Response

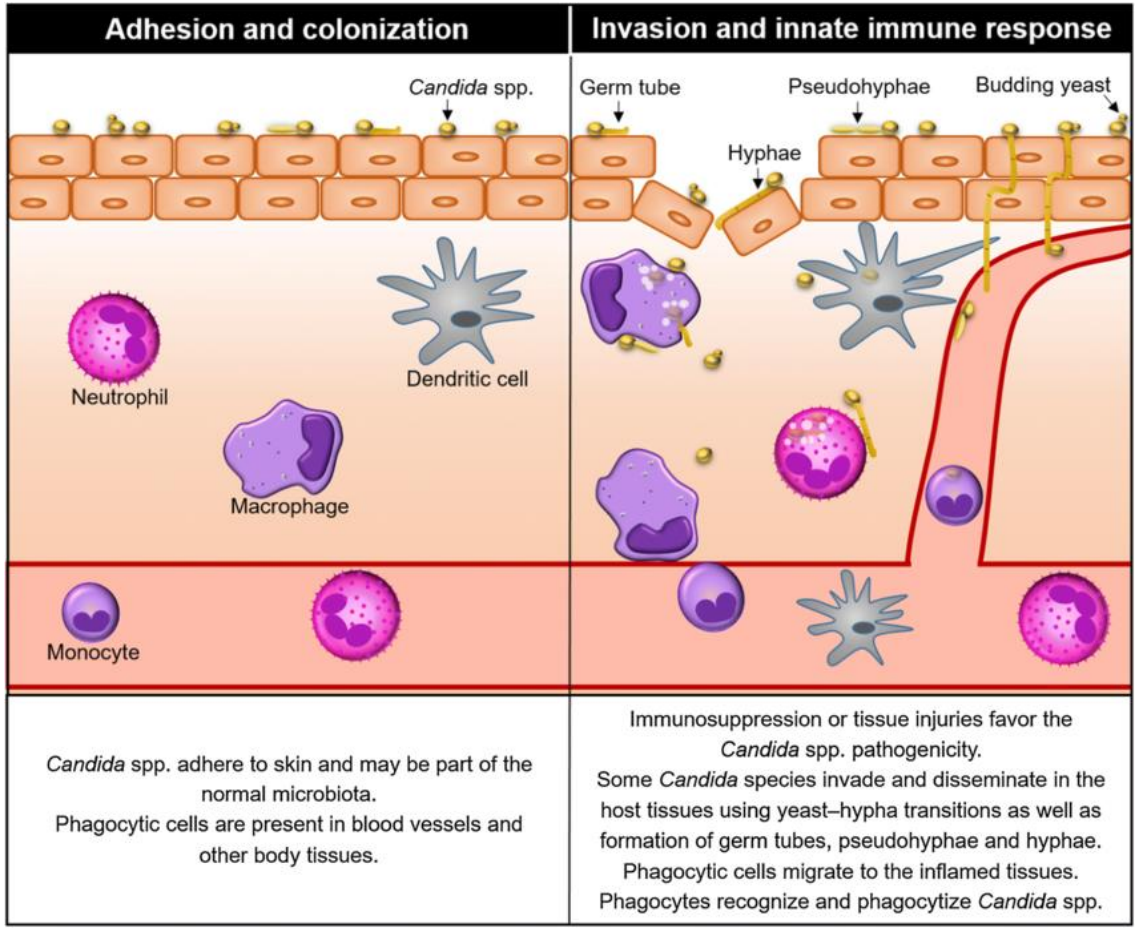
Mechanisms of immune evasion by mycobacteria

- Engulfment via complement receptors – avoids triggering respiratory burst,
- Inhibition of macrophage activation by lipoarabinomannan
- Inhibition of phagolysosome formation,
- Invasion of macrophage cytoplasm – provides protection from killing by phagolysosome,
- Invasion of non-professional phagocytes, e.g. Schwann cells by M. leprae.



Mechanisms of Immunity to Fungal Infections

- Fungi cause many diseases, which can be classified into superficial, subcutaneous or deep mycoses.
- In superficial mycoses, the skin or mucous membranes are the main sites of the attack, while subcutaneous mycoses involve adjacent tissues, such as skin or bone.
- Fungi causing systemic infections are usually divided into two groups: pathogenic and opportunistic fungi.
- Candida infection has been chosen as an example in this discussion, since it is an ubiquitous fungus which frequently causes superficial infection in normal hosts.



Parasitic Evasion of Immune Defenses

Mechanism	Parasite example(s)
Antigenic variation	*Trypanosoma brucei* *Plasmodium* merozoites
Evasion from macrophages	
Prevention of lysosome-phagosome action	*Toxoplasma gondii*
Prevention of lysosomal toxic action	*Leishmania* amastigotes
Escape into cytoplasm	*Trypanosoma cruzi*
Resistance to complement lysis	*Leishmania, T. brucei,* *T. cruzi, Taenia solium*
Immune suppression	Filariae
Surface and secreted antioxidant enzymes	Parasitic nematodes, schistosomes

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