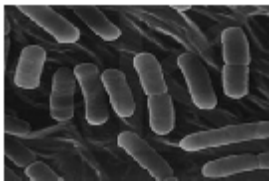
The goal of a balanced immune system

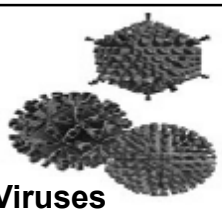
- Pathogens
- Tumor cells
- Autoimmunity or Allergy

Immune responses to Pathogen

The Invaders . . .

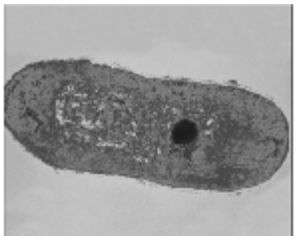
Bacteria



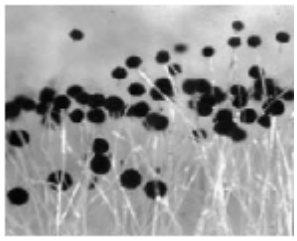


Viruses

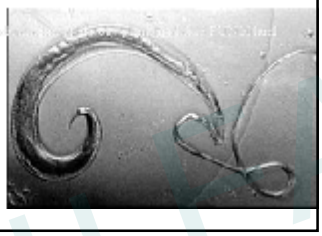
Parasites



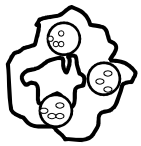
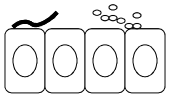
Fungi

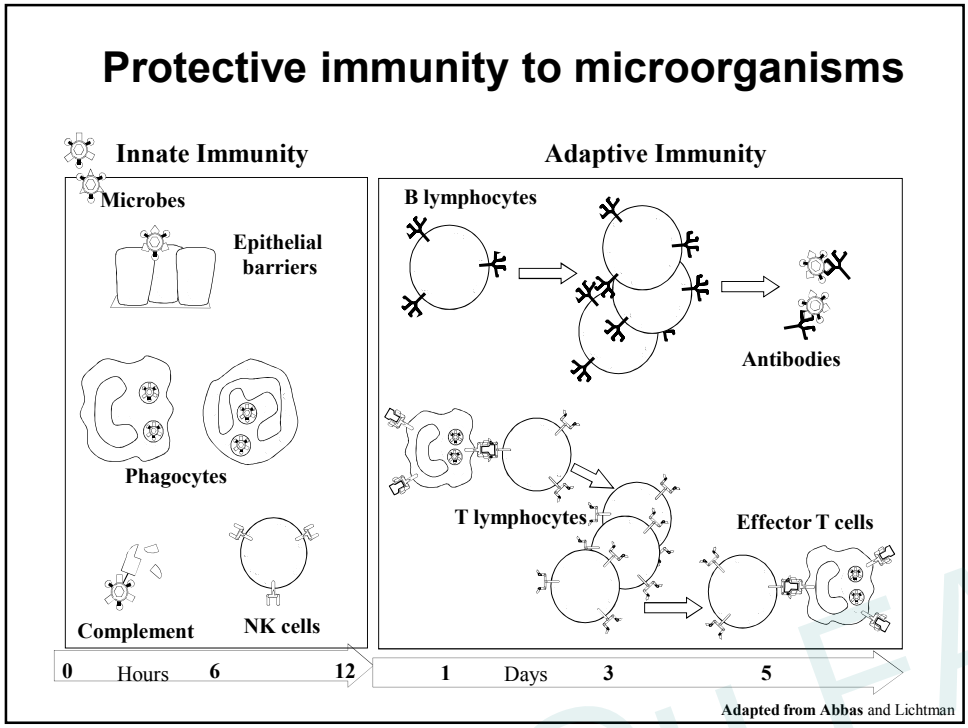


Worms

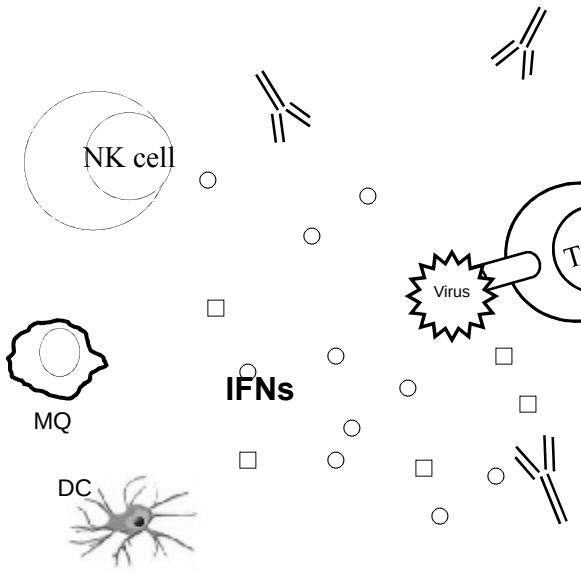


Pathogens in various compartments

	Intracellular		Extracellular	
				
Site of infection	Cytoplasmic	Vesicular	Interstitial space blood, lymphs	Epithelial surfaces
Protictive immunity	Cytototic T cells ADCC NK cell	T cell dependent Macrophage activation	Antibodies Complement Phagocytosis Neutralization	Antibodies, especially IgA, Inflammatory cells
Micro-organisms	Viruses Chlamydia Listeria protozoa	Mycobacteria Salmonella Leishmania Trypanosoma Legionella….	Viruses Bacteria Protozoa Fungi Worms	Neisseria gonorrhoeae Worms Candida Streptocouccs Vibrio cholerae Escherichia coli



Immune response to virus

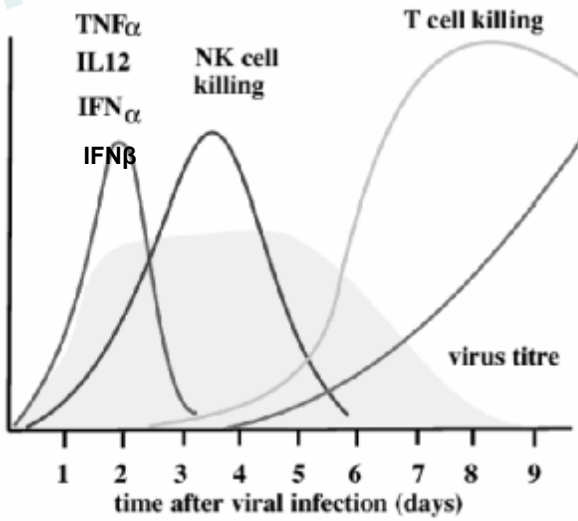


Early immune defenses:
interferon, NK cells, and macrophages DCs

Humoral immunity:
Antibodies

Cell mediated immunity:
CD8,CD4

Kinetics of host defenses in response to a typical acute virus infection



NK cells& interferon are detected in the blood and infected tissues.

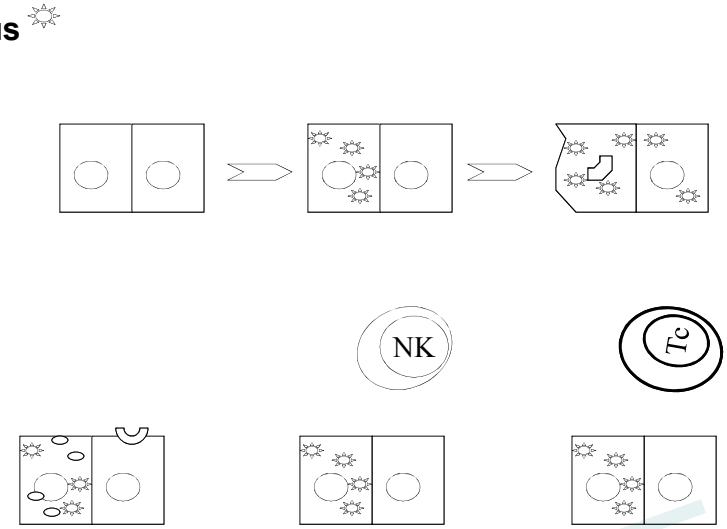
CTLs:lymph nodes or spleen, Neutralizing Abs serum.

activated T cells are absent by the 2 to 3 week,

T cell memory is established and may last for many years.

Immunity and immunopathology

Virus



Interferons

- Small proteins released by virally infected cells Trigger the production of antiviral proteins
- Two types of IFNs:

Type I IFNs

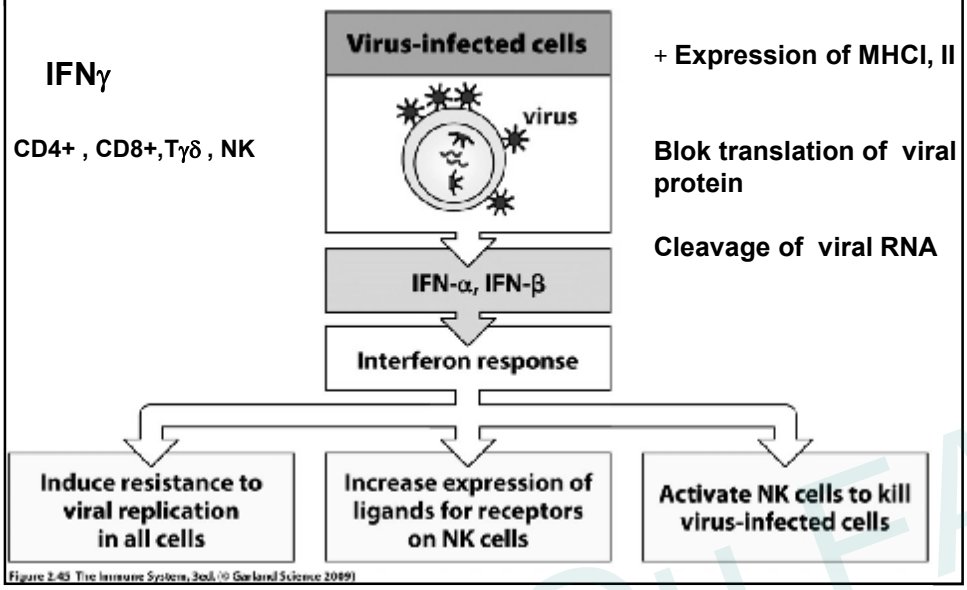
Alpha: produced by leukocytes and attract/stimulate NK cells
Beta: secreted by fibroblasts causing slow inflammation

Type II IFN

Gamma: produced following antigenic or mitogenic stimulation of T and NK cells. Stimulate macrophage activity.

- Interferons exert antiviral activity by a variety of mechanisms

Roles of IFNs



Anti-Viral Immunity

Anti-viral activity of interferons (IFNs)

- Virus infected cells produce INFs

- INF-α inhibit intracellular replication of viruses

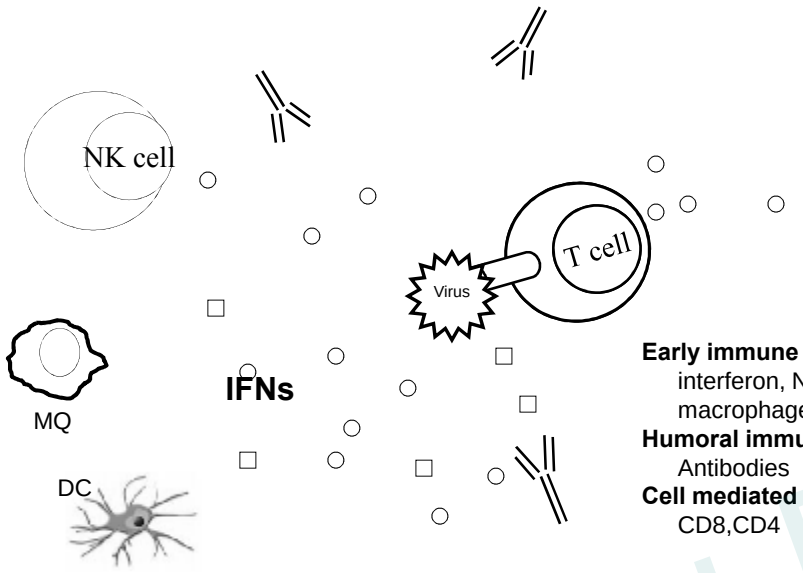
- IFN-α activate NK-cells and macrophages to kill virus infected cells

- IFNs have no direct effect on extracellular virus

- IFNs act early in viral diseases before antibody

- INFs activity is not specific

Immune response to virus



Early immune defenses: interferon, NK cells, and macrophages
Humoral immunity: Antibodies
Cell mediated immunity: CD8,CD4

Antibodies

- Antibodies provide a major barrier to virus spread between cells and tissues and are particularly important in restricting virus spread in the blood stream.
- IgA production becomes focused at mucosal surfaces where it serves to prevent reinfection.
- Antibodies may be generated against any viral protein in the infected cell.

Anti-Viral Immunity
Roles of antibodies

- In viraemic infections, antibodies neutralize virus, preventing its attachment to receptor sites on susceptible cells (e.g. Poliovirus, mumps, measles, rubella)
- In superficial non-viraemic infections (infleunza)

  Secretory **IgA** neutralizes virus infectivity at the mucous surfaces
- Antibodies destroy free virus particles directly by aggregation of virus and opsonization or by complement mediated lysis
- Both mechanisms also act on virus infected cells

Antiviral effects of antibody

target	agent	mechanism
free virus	antibody alone	blocks binding to cell blocks entry into cell blocks uncoating of virus
	antibody + complement	damage to virus envelope blockade of virus receptor
virus-infected cells	antibody + complement	lysis of infected cell opsonization of coated virus or infected cells for phagocytosis
	antibody bound to infected cells	ADCC by NK cells, macrophages, and neutrophils

ADCC, antibody-dependent cellular cytotoxicity

The stupidest virus is cleverer than the cleverest virologist

Viruses might be very tiny and have no brains, but when it comes to survival games no one can call them dumb

How can a virus evade the immune system

Antigenic variation

- involves mutating regions on proteins that are normally targeted by Abs and T cells.
- human immunodeficienc virus (HIV): (mutations) can arise in those viral peptides that bind to MHC class I molecules to which the initial T cell response arose.
- is responsible for the antigenic shift and drift seen with influenza virus.
- Humoral immunity to such diseases lasts only until the new virus strain emerges,making effective longlasting vaccinations difficult to produce.

Failure of T cell surveillance and the emergence of new pathogenic variant viruses.

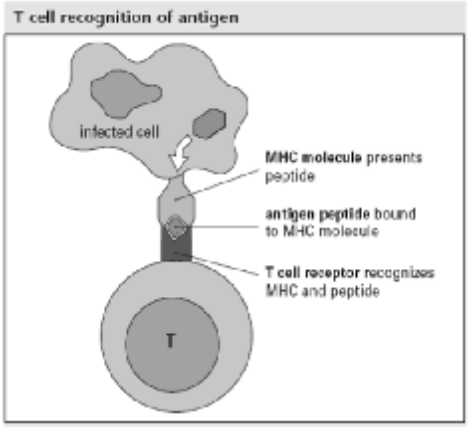
How can a virus evade the immune system

Strategies to control the expression of MHC molecules

MHC class I expression can be disrupted by:

- blocking peptide uptake into the endoplasmic reticulum
- preventing maturation assembly and migration of the MHC complex.
- other mechanisms involve premature targeting of MHC class II for degradation.
- Downregulation of MHC class I may disrupt CD8+ T cell recognition.

What advantage is there for a virus in causing the loss of MHC class I molecules in the cell it has infected?



The infected cell can no longer be recognized by cytotoxic T cells

How can a virus evade the immune system

Strategies for disrupting the chemokine network.

Chemokines represent an important traffic-light system for cell migration

- The herpesviruses encode chemokine homologs (e.g. CCL3);
- chemokine receptor homologs; and chemokine-binding proteins, which have powerful effects on delaying or inhibiting cell migration during inflammation.

- viruses encode homologs for CD46 and CD55 – complement regulatory proteins that block C3 activation.

  HIV makes use of cellular CD59, which is incorporated in the viral envelope, thereby blocking complement mediated lysis of the virion.

How can a virus evade the immune system

Strategy for disrupting the interferon system.

- Interference with interferon signaling.

- Some can produce their own cytokines so they compete with the human ones and confuse the immune response.

- They can produce receptors for human cytokines to remove them quickly from the infection site and mute the “call-to-arms”.

Responses to viral antigens can cause tissue damage

The formation of immune complexes

- Immune complexes may arise in body fluids or on cell surfaces and are most common during persistent or chronic infections (hepatitis B virus)
- Immune complexes form and are deposited in the kidney or in blood vessels, where they evoke inflammatory responses (glomerulonephritis).

Responses to viral antigens can cause tissue damage

CTL responses can cause sever tissue damage

chronic active hepatitis in humans, whereby CTLs target hepatitis B virus-infected cells and may also participate in a nonviral autoimmune disease.

Responses to viral antigens can cause tissue damage

Viruses can infect cells of the immune system

- ***HIV infects CD4+ cells***
- prolonged clinical latency
- ineffective immunity
- continuous virus mutation
- neuropathology and a tendency to infect bone marrow-derived cells and lymphocytes .

- HIV is taken up by CD4+ T cells and macrophages following binding of a viral glycoprotein (gp120) to CD4 and certain chemokine receptors (CXCR4 and CCR5).

- It also enters other antigen-presenting cells by this route