

# *Immune Response to infections & tumors*

*Prof. Sunil-Chandra*

*20.08.2015*

# *Immunity to infection*

- We are engaged in constant warfare with the microbes.
- Immunity to infection depend on the Processes of mutation & evolution that
  - select microbes which evolved means of evading our defense mechanism.
  - select hosts which evolved means of defense against pathogenic microbes

# Intracellular vs Extracellular Life: choices & consequences

- Most pathogens have evolved to live either inside or outside of host cells, rarely in both habitats.

# Intracellular life

## 1. Poses special problems for host;

- host can't easily attack pathogen without harming its own tissues.
- Many pathogens are adapted for intracellular life, i.e. **all viruses, certain bacteria (e.g. TB, plague),**

## 2. Since white blood cells (macrophages, lymphocytes) are major components of defense system, **many successful pathogens target macrophages, lymphocytes specifically for intracellular growth.**

## 3. **Problem: to be successful, pathogen at some point must leave cells, exit host. Best chance to prevent infection** is sometime during exit -- transmission -- entry to new host, before it has a chance to hide in new cells.

## 4. Some intracellular parasites are so highly evolved that they can't survive at all outside their host's cells. Ex: ***Chlamydia, Rickettsia***. **To be successful, these must rely on mechanisms such as sexual contact or animal bites to transmit them to new hosts.**

# Facultative intracellular pathogens

- Some bacteria can grow either inside host cells or outside, depending on circumstances.

Examples: *Shigella*, *Salmonella* sp.

# **Virulence Factors**

- Virulence Factors are specific adaptations that allow pathogen to:
  - Attach selectively to host tissues
  - Invade or destroy host tissues to gain access to nutrients
  - avoid host defenses
- Many examples of virulence factors:
  1. Specific attachment & entry factors
  2. Invasive enzymes
  3. Strategies to avoid host defenses
  4. Exotoxins
  5. Endotoxins
  6. Siderophores

# Host Defenses

## Nonspecific Host Defenses

- 1. Mechanical/Physical barriers
  - Tissue barriers (Skin & mucosal surfaces)
- 2. Chemical barriers
  - corticosteroids, etc
- 3. Phagocytes
- 4. Inflammation

## Specific/adaptive Host Defenses

- Two arms of immune response:
- 1. Humoral
  - 2. Cell Mediated Immunity
- (a). Naturally acquired
- Active
  - Passive
- (b). Artificially acquired
- Active
  - Passive

- Immunity to viruses
- Immunity to bacteria
- Immunity to fungi

# Immunity to viruses

**Immune response may vary from**

- (1). apparently non –existent
- (2). Life long immunity
- (3). Chronic immunopathology

# Immune response to viruses

- Response to viral Ags almost entirely T cell dependant
- Viral internal Ags do not induce protective immunity
- Viral Ag express on surface induce protective immunity

# Possible mechanisms available to combat different phases of generalized virus infections

1. **Interferon** (1<sup>st</sup> line of defense)
2. **Secretary IgA** of epithelial cell surfaces.
3. **Serum antibody** (IgM & IgG) - viruses in viraemic phase are susceptible.
4. Variety of cellular & humoral mechanisms.
  - **T cells / NK cells**
  - **Complement**

# Possible mechanisms - generalized virus infections

- **Antibody** bind directly to extracellular viruses.
  - IgG & IgM - action limited to Plasma & Tissue fluid
  - IgA - protect - epithelial surfaces.
- **Antibody** in association with complements (C1 - C9)
  - Lysis of cells carrying viral Ag
  - Direct damage to enveloped viruses
- **Cytotoxic T cells (Tc) & Antibody dependent cytotoxic cells (i.e. NK cells)**, effective against intracellular viruses.

# **Effects of Antibody**

**Antibody important in cytolytic viruses**

## **1. Disrupt virus - cell interactions**



Adsorption  
Penetration  
Uncoating  
Replication

## **2. Antibody binding to critical sites (i.e HA in influenza virus).**

## **3. Ab-Ag complexes activate complement.**

Complement binding assists in;

Neutralization by coating

Lysis of lipid membranes (complement lysis of enveloped viruses)

# Effects of Antibody

4. Antibody dependent cytotoxic cells.

Provide a clear cut protection for viral infections of long incubation period.

i.e. **Poliomyelitis** - ADCC K cells are involved;

Act by binding to specific Ab on infected cells via FC receptors.



Kill infected cells

# Effects of Tc & MHC restriction

- Important for intracellular organisms such as viruses
- T cell memory cause rapid response
- **Intracellular viruses** which bud off to adjacent cells without exposure to Ab. (antibody important in cytolytic viruses which become extracellular).  
i.e. Influenza virus.

Mumps

Measles

Rabies

Herpes

HSV

VZV

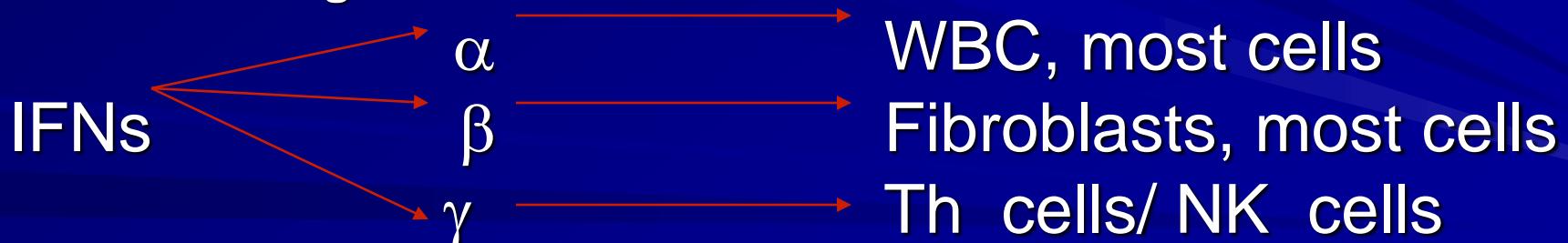
CMV

EBV

**CMI is important**

# Interferons

- Produced by many cell types **in response to viral infections.**
- Cell types also produce IFN **in response to**
  - ds RNA
  - Endotoxins
  - Variety of stimuli
    - Mitogenic
    - Antigenic



# **Immunity to bacteria**

## **1. Nonspecific barriers;**

Intact skin, fatty acids

Epithelial cell surfaces are cleansed by  
-ciliary action of upper respiratory tract

Flushing of urinary tract

pH changes in Stomach & Vagina

## **2. Commensals in some sites of the body**

## **3. Once bacteria gain entry, compliment, phagocytes & adaptive immunity important - depend on**

-Bacteria spp: involved.

-Host ability to damage components of  
bacterial cell wall (depend on cell wall types)

# Cell wall types & other structures

- 1. Gram + ve cell wall
- 2. Gram - ve cell wall
- 3. Mycobacterial cell wall
- 4. Spirochetal cell wall
  
- Other surface structures
  - Fimbriae
  - Flagellae
  - Protein
- Capsules

# Non specific mechanisms involved in bacterial immunity

1. Activation of alternate complement pathway  
Complement deposition



Opsonization



Phagocytosis

*Cont..d.*

*Cont..d.*

2. Complement-activation → attract PMN  
PMN → release lactoferrin



Take up iron



Inhibit bacterial growth

3. C3a,C5a → chemotactic agents for

PMN  
Mφ

Trigger mast cell degranulation

*Cont..d.*

*Cont..d.*

#### 4. Tissue injury by bacteria

Clotting → Fibrin → Prevent spread

#### 5. Kinin

PG

Leucotrienes

} mast cell degranulation  
increased blood flow  
increased  
capillary permeability

# Interaction of phagocytes

Attraction



attachment



phagocytosis



killing

**Refer – innate immunity Lecture for  
Killing mechanism of PMN and M $\phi$**

1. Non oxygen dependent killing
2. Oxygen dependent killing

# Specific mechanisms involved in bacterial immunity

## Role of Ab:

1. Coating with Ab improves phagocytosis
2. Some organisms have receptors for epithelial surfaces
  - Group A streptococci
  - Gut pathogens
- These receptors can be blocked by Abs.
3. Neutralize streptococcal M.Proteins which inhibit phagocytosis.  
Similar action on capsules i.e.meningococcal capsule.

# Defense mechanisms in bacterial infections

Relate to the nature of organism & the disease caused by;

- Pathogenicity of some non invasive infections of epithelial surfaces depend on;
    - Toxins → *C:diphtheriae*
    - Adhesion → *V: cholera*
  - Defense →
    - neutralizing Ab to toxin
    - Ab to block adhesion to epithelial surfaces
- cont..d.*

*cont..d.*

■ **Pathogenicity of invasive organisms.**

Does not depend on toxins, therefore immunity is required to kill bacteria.

1. G-ve bacteria

**Ab + complement lytic pathway kill bacteria with lipid membrane. e.g. *N:meningitides***

2. G + ve bacteria

**Opsonization and specific immunity by Ab (Ab + C') (lytic pathway irrelevant)**



killed by phagocytic cells

e.g. *S: aureus*

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- Intracellular bacteria

- Resist killing by phagocytes

- Killed by Mφ stimulation by T cell products (cytokines)

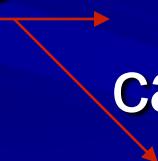
- e.g. *M. tuberculosis*

- M. laprae*

- Listeria*

- Brucella*

# Evasion of bacterial killing mechanisms

1. Some bacteria prevent the arrival of phagocyte by secreting toxins.  
(exotoxins block inflammatory activity & chemotaxis).
2. Resist phagocytosis  
Poor activators of C'      
  - capsule of *Neisseria*.
  - M protein of *S. pyogenes*.

*cont..d.*

3. Once phagocytosed, different mechanisms resist killing

- Prevent fusion between phagosome & lysosome.  
e.g. *M.tuberculosis*
- Intensify the resistance of cell wall or ability to neutralize
  - $\text{H}_2\text{O}_2$
  - Superoxide
  - Antibacterial proteins

4. Colonization of external surfaces avoid provocation of phagocytes.

# Immunity to fungi

- Little is known

## Four major fungal infections in man

- Superficial mycoses
- Subcutaneous mycoses
- Respiratory mycoses
- Candidiasis

*cont..d.*

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## Cutaneous fungal infections

- Usually self limiting
- Recovery associated with limited resistance to reinfection based on CMI.
- Patients develop DTH to fungal Ags.
- Resistance can be transferred by immune T cells.

## Respiratory mycoses

- DTH (type iv) activity

*cont..d.*

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## Candidiasis

- Disturbance of normal physiology or abnormality in normal flora predispose invasion by Candida.

In general Fungal infections T cell immunity is more important.

# *Immune Response tumors*

Physiological function of immune system is to eradicate tumors and prevent the growth of tumors.  
This phenomenon is - **immune surveillance**

# Immune response to tumors:

- (a). Tumor antigens
- (b). Immune mechanisms of tumor rejection
- (c). Evasion of immune responses by tumors
- (d). Immunological approaches for cancer therapy

# Evidence supporting immune system protect against tumours

## Evidence

### ■ Histopath & Clinical observations:

Lymphocytic infiltrates around tumours

Enlargement of draining lymph nodes.

## Conclusion

- inhibit tumour growth
- Better prognosis

### ■ Experimental:

Transplant of tumours are rejected by

Animals previously exposed to that tumour.

Immunity can be transferred by lymphocytes from a tumour bearing animals.

- tumour rejection shows Specificity & memory, mediated by lymphocytes

### ■ Clinical & Experimental

Immunodeficient persons have increased

Incidence of some types of tumors

- immune system protect against tumors (“immune surveillance”)

# Immune response against tumors.

## Innate immunity:

- Macrophages, dendritic cells
- NK cells

## Acquired immunity:

- (1). Immune surveillance to virus induced tumors  
i.e. EBV, immunosuppression lead to tumor growth
- (2). Activity of tumor specific Th and Tc cells detected in patients with different types of tumors.

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# Tumour antigens

If the immune system react against tumour of an individual, Tumour must express Ags seen as “non-self”

Tumor antigens may be products of

- (i). oncogenes,
- (ii). Tumour suppressor genes,
- (iii). Mutated cellular proteins,
- (iv). Overexpressed or aberrantly expressed molecules (i.e. self proteins express only in embryonic tissues but if express in tumours) or
- (v). products of oncogenic viruses.

# Types of tumour antigens recognized by T cells

## ■ Mutated self protein

- carcinogen or radiation induced tumours, i.e. melanomas

## ■ Product of oncogene or mutated tumour suppressor gene

- Oncogene products (mutated Ras, Bcr/Abl fusion proteins)
- Tumour suppressor gene products (mutated p53 protein)

## ■ Over expressed or aberrantly expressed self protein

- Tyrosinase, gp 100, testis antigens

## ■ Oncogenic virus

- Human papillomavirus E6, E7 proteins in CA cervix,
- EBNA proteins in EBV induced lymphomas

# Examples Tumor antigens:

- Common acute lymphoblastic leukaemia antigen (CALLA)
- Oncofetal antigens i.e. alpha –fetoprotein (AFP) produced by liver cancer cells
- Carcinoembryonic antigen (CEA) produced by colon cancer cells and other epithelial tumours

# Immune mechanisms of tumor rejection

## Tumor rejection is mediated mainly by

- CTLs recognizing peptides derived from tumor antigens.
- The induction of CTL responses against tumor antigens often involves
  - (i). Ingestion of tumor cells or Ingestion of antigens of tumor cells by dendritic cells
  - (ii). Presentation of the antigens to T cells.
  - (iii). Differentiation of tumour specific T cells
  - (iv). Tumour specific CD8+ CTL recognizes tumour cell
  - (v). CTLs kill tumor cells without co-stimulation of T cell help

# Evasion of immune responses by tumors

Tumors may evade immune responses by

- (i). losing expression of tumor antigens
- (ii). Shutting off expression of MHC molecules or
- (iii). Shutting off molecules involved in antigen presentation,
- (iv). Secreting cytokines that suppress immune responses.

# How tumours evade immune responses?

- **(i). Failure to produce tumor antigen:** → Antigen loss variant of tumour cell
  - lack of T cell recognition
- **(ii). Mutations of MHC genes or genes needed for Ag processing:** → Class- 1 MHC deficient tumour cell
  - inability to present tumor Ag- peptides.
  - lack of T cell recognition
- **(iii). Production of immunosuppressive molecules** → inhibitory cell surface proteins, immuno-suppressive cytokines (i.e. TGF $\beta$ )
  - Inhibition of T cell activation

# How tumour cells evade immune responses?

- (iv). **Absence of B7 co-stimulation;**
  - Induction of immune response need co-stimuli from B7 molecule present in specialized APCs . Presentation of MHC-peptide antigen complex to TCR in absence of B7 co-stimulation lead to anergy of tumour infiltrating lymphocytes.
    - lack of T cell recognition
- (v). **Tumor cells lack other molecules** required for adhesion of lymphocytes such as LFA-1, LFA-3, oe ICAM-1.
- (vi). **They may express mucin** which can be anti-adhesive

# Immunological approaches for cancer therapy

Immunotherapy for cancer aims to enhance antitumor immunity by

- (i). Passively providing immune effectors to patients or
- (ii). By actively boosting the host's own immune effectors.
  - Approaches for active boosting include vaccination with **tumor antigens** or with **tumor cells engineered to express co-stimulators or cytokines**

# **Self study : Tumours of the immune system**

## **1. Multiple myeloma**

- What is multiple myeloma and how is the diagnosis is made?
- What are Bence -Jones proteins?
- Explain Immunological basis of anaemia and recurrent bacterial infections in patients with multiple myeloma.

# Self study : Tumours of the immune system

## **Acute lymphoblastic leukaemia (ALL)**

- What is acute lymphoblastic leukaemia (ALL)?
- How can immunophenotyping of malignant cells aid in the diagnosis of ALL?