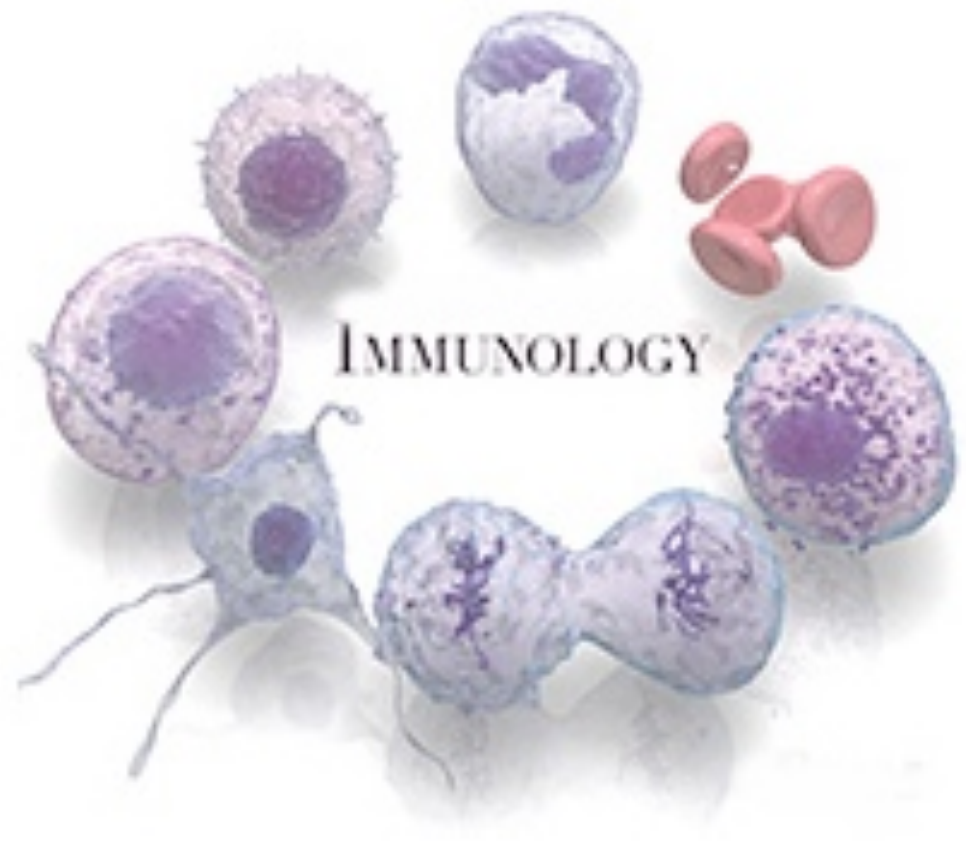

Immunology of TB

429 immune Team:

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* It is estimated that almost 2 billion people worldwide are infected with *Mycobacterium tuberculosis*.

* T.B. is an example of an infection in which **protective immunity? & Pathologic hypersensitivity** coexist, and the lesions are caused mainly by the host response

TB is a clinical example for delayed type hypersensitivity (Type Iv).

The incidence has recently been increasing due to:

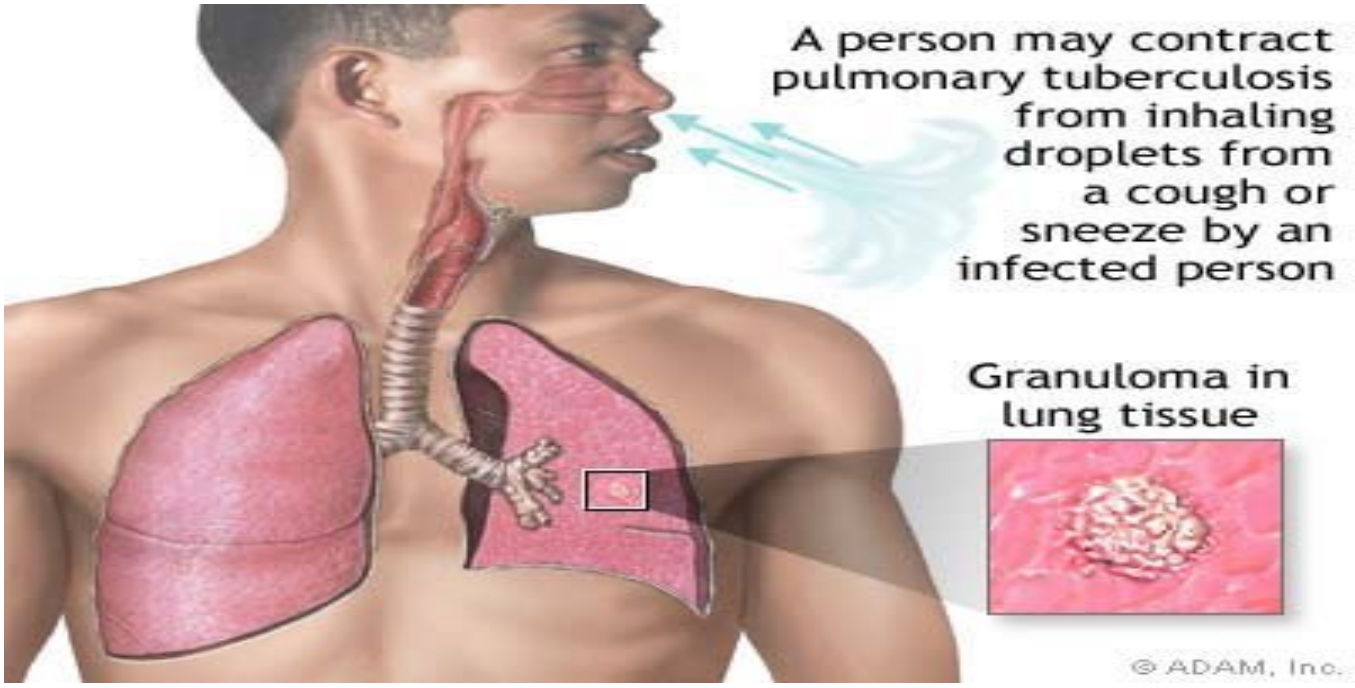
* Emergence of antibiotic resistant strains

* Increased incidence of immunodeficiency caused by HIV infections

* Immunosuppressive therapy

TB is a chronic infection, which is characterized by granuloma formation, and the granuloma may undergo CASOUS NECROSIS.

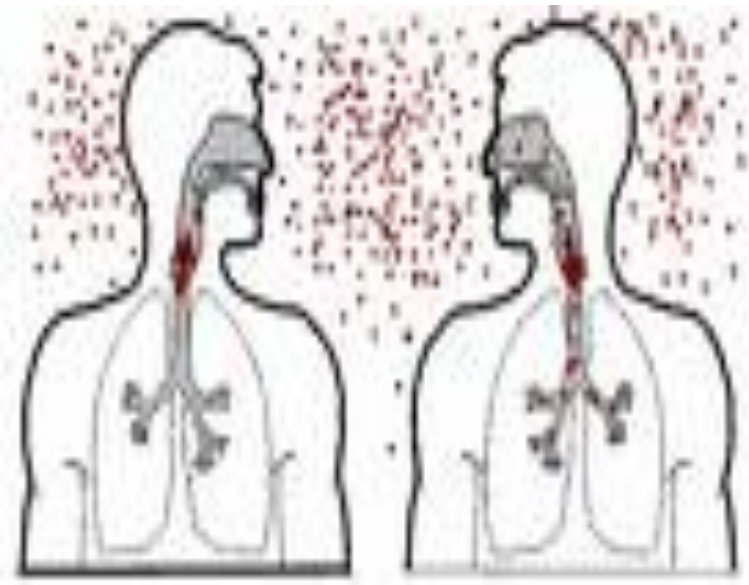
** As these caseous lesions heal, they become calcified and are readily visible on x-rays, where they are called Ghon complexes. ??



Mode of transmission:

Infection is acquired by inhalation of *M. tuberculosis* in aerosols and dust

(Airborne transmission)



Infected people cough up large numbers of mycobacterium into the environment ⇒ the organisms have waxy outer coats therefore can withstand drying and survive for long periods in air and house dust.

Primary infection

(infections in individuals for the first time)

organisms are inhaled from air or dust

→

engulfed by alveolar macrophage (non-resident macrophages are also attracted)

→

macrophages ingest the pathogens and carry them via the lymphatics to the local (hilar) lymph nodes

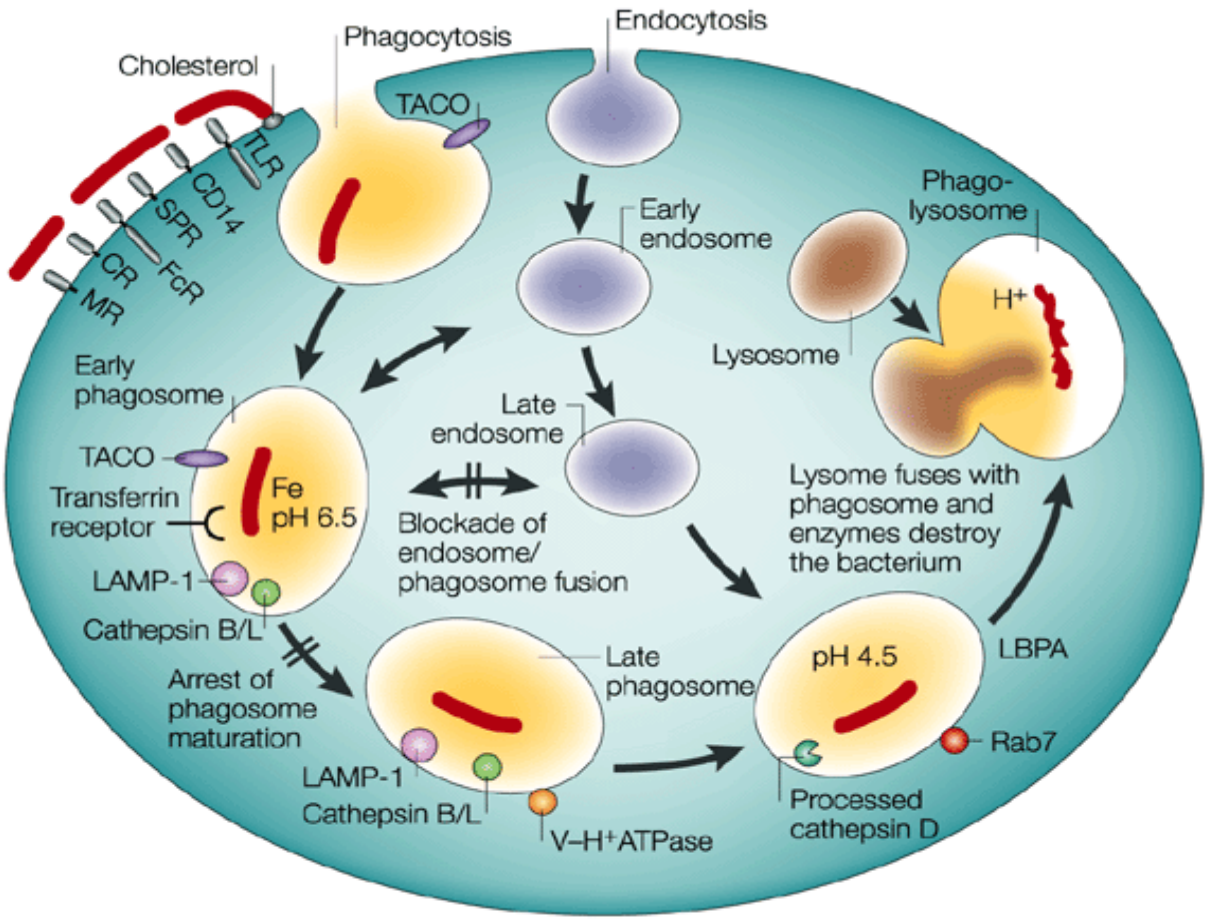
Mycobacterium tuberculosis stimulates macrophages by binding Toll-like receptors.

- These receptors recognize
- Mycobacterium lipoproteins &
- Polysaccharides

(From the mycobacterium cell wall)

This stimulate:

- phagocytosis.
- Secretion of cytokines



Mycobacterium persist inside macrophages:

- Waxy coat block the effect of phagocyte enzymes

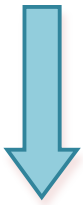
-Mycobacterium also secretes catalase, which prevent the effects of the respiratory burst.

(Respiratory burst is the secretion of the oxygen & nitrogen radicals by macrophages and neuotrophils to kill the mycobacterium)

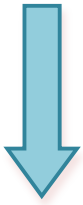
- Mycobacterium hide inside phagososmes of the infected macrophage.

Mycobacterial peptides presented by macrophages

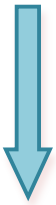
(peptides from the cell wall of the mycobacteria)

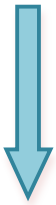


elicit strong T helper (TH1) response



activated T-cells secrete cytokines





tumor necrosis factor

(TNF)

interferon-gamma

(IFN-γ)

***** Th1 cells are responsible for CMI, which is required for handling mycobacterium tuberculosis.**

By 6 -8 weeks after infection:

**Infected Macrophages localize in the draining lymph nodes, this will activate CD4 T-cells and secrete IFN-gamma.

**After, CD8 T-cells become activated later, which will activate infected macrophages.

Q/ why infected macrophages ?

A/ to enhance their ability to kill phagocytosed bacilli (because it is hard to kill mycobacteria that are sealed in phagososmes) , in other words the infected macrophages need support (more cytokines) to kill the mycobacterium , and if that didn't work the CD8 cells will directly kill the infected macrophage.

- Activated T-cells and activated macrophages secrete tumor necrosis factor (TNF), it plays a role in:

1- Local inflammation.
2- Further macrophage activation.

The resulting T-cell reaction (CMI) adequate to control bacterial spread (bacilli are contained within tubercles)

Delayed type hypersensitivity reactions (DTH) occur as:

1- Collateral damage during a protective response to a microbe.
2- DTH may be entirely pathologic as in certain autoimmune disease.

- ## DTH reactions in tuberculosis:

  Chronic DTH reactions develop when the TH_1 response to mycobacteria activates macrophages but fails to eradicate phagocytosed microbes, and this will lead to granulomatous inflammation (which is a form of DHT reactions to the bacilli).

- ## Changes of macrophages in response to cytokines in chronic DTH:

  They develop increased cytoplasm and become epithelioid cells, and fuse to form multinucleated giant cells, which surround the ingested bacilli to form part of the granuloma.

- ## Granulomas may undergo central necrosis (caseous necrosis):

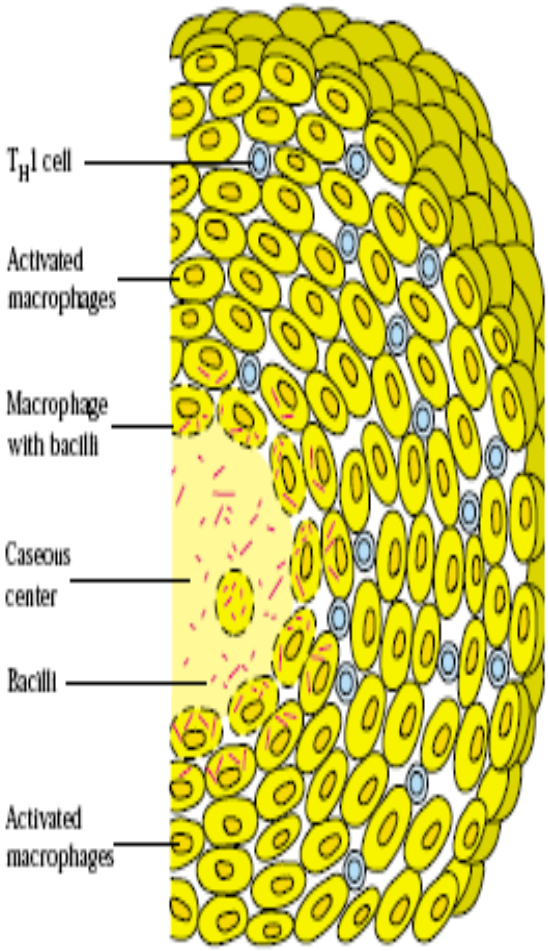
  Necrosis result from macrophage products:

  a. Lysosomal enzymes.
  b. Reactive oxygen radicals.

  Necrosis serves to eliminate infected macrophages and provide an anoxic environment in which bacilli cannot divide.

  (Even the injured tissue may give protective function)

A tubercle consists of a few small lymphocytes and a compact collection of activated macrophages, which sometimes differentiate into epithelioid cells or multinucleated giant cells. The massive activation of macrophages that occurs within tubercles often results in the concentrated release of lytic enzymes. These enzymes destroy nearby healthy cells, resulting in circular regions of necrotic tissue, which eventually form a lesion with a caseous (cheese- like) consistency. As these caseous lesions heal, they become calcified and are readily visible on x-rays, where they are called Ghon complexes.



- **Outcome of primary infection " depends on the immune state of individuals ":**

1- Complete healing.
2- Progressive infection.
3- Excessive response to primary infection.
4- Post primary (reactivation).

5% progressive infection

90% remain asymptomatic.

5% reactivation.

**In most patients 90 % , primary infection heal to leave a small visible scar on radiograph.

(mycobacteria remain alive inside macrophages)

This is called The Ghon complex (primary complex)

- **The Ghon complex consist of:**

The lung lesions (tubercles-small granulomas) + the enlarged lymph nodes.
Tubercles may heal become fibrotic or calcified and persist as such for a lifetime.
(Shows on chest x-ray as radio-opaque nodules)

In individuals with impaired immunity

Mild immunodeficiency

Lead to reactivation, usually in the apices of the lung

severe immunodeficiency

Leads to more widespread infection beyond the lungs.

*In-patient with excessive TNF production, lesions cans breakdown leading to open T.B.

*In small proportion of young patients, widespread primary T.B occur. May present as: ***miliary T.B (or) tuberculosis meningitis***

Reactivation of dormant mycobacteria is usually a consequence of impaired immune function resulting from:

1- Malnutrition.
2- Infection (e.g.: AIDS)
3- Chemotherapy for treatment of tumors.
4- Corticosteroids for treatment of inflammatory disease.

Test for immunity against T.B:

(Delayed hypersensitivity skin test.)

- The delayed hypersensitivity skin test assess immunologic memory to mycobacterium (T-cell recall response)

- The test is known as: **Tuberculin test**, or (Mantoux)

  - The test is carried out with: Intradermal injection of PPD (purified protein derivative)

Mechanism of tuberculin test:

- Toll-like receptors on dermal macrophages recognize mycobacterium and secrete:

  TNF & Chemokines.

  - - Dendritic cells (loaded with mycobacterium antigen) migrate from site of injection to draining lymph nodes & activate primed T-cells
  - -Then, activated T-cells migrate to injection site and interact with activated macrophages.
  - - The cytokines released produce: erythema and induration at the site.

Outcomes of tuberculin test

-ve may be due to:	+ve may be due to:
Immunodeficiency (secondary to HIV)	BCG vaccination
Never been vaccinated or exposed to myco. TB (rare)	Recent exposure to T.B

How to do it?

After intradermal injection of PPD measure diameter of induration after 48 hours

Blood test for T.B. exposure:

- The blood test measures interferon – gamma secreted in response to mycobacterium antigen

- Mycobacterium peptides are added to the patient's blood, which is then incubated for 12 hours.

The amount of (IFN) produced is then measured by ELISA test

Prevention:

1. Immunoprophylaxis vaccination.

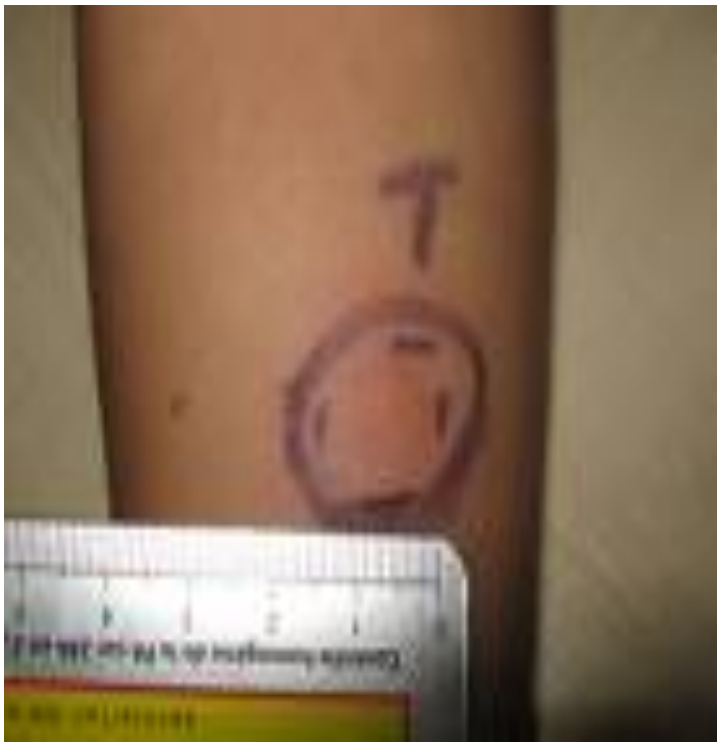
2. Chemoprophylaxis anti- tuberculosis drugs: (Drugs taken before potential exposure to myco. TB, e.g. traveling to infected area)

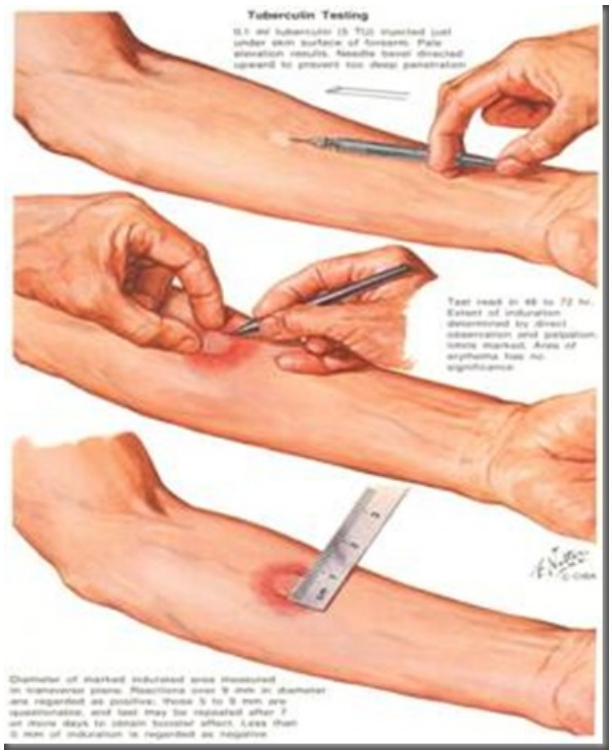
Immunoprophylaxis:

- B.C.G. Vaccine (Bacillus Calmette Guerin): is a live attenuated non-virulent strain of M. bovis

- BCG has been used effectively in situations where tuberculosis is prevalent.

- Immunization does not prevent infection but allow the body to react quickly to limit proliferation of the organism.

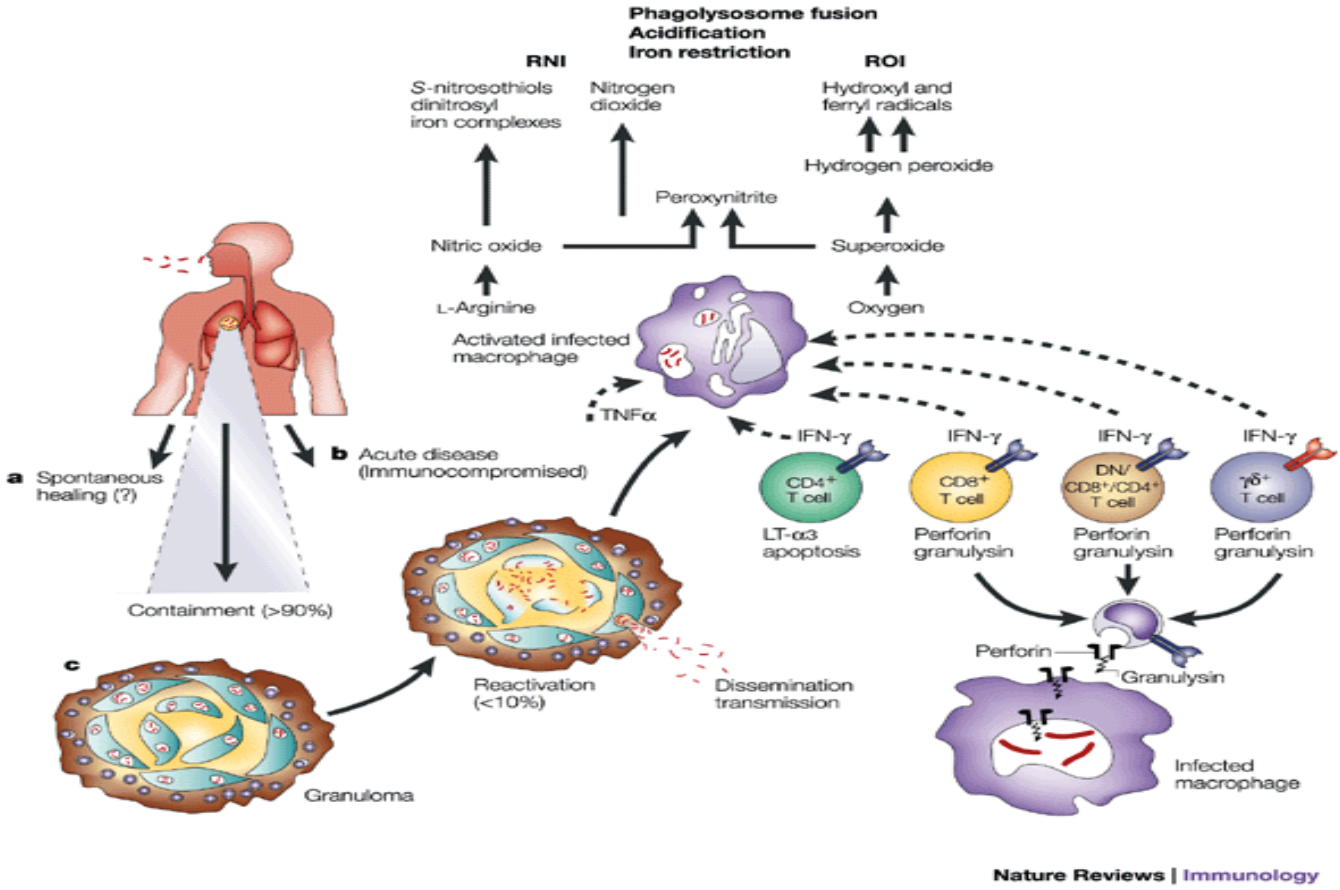


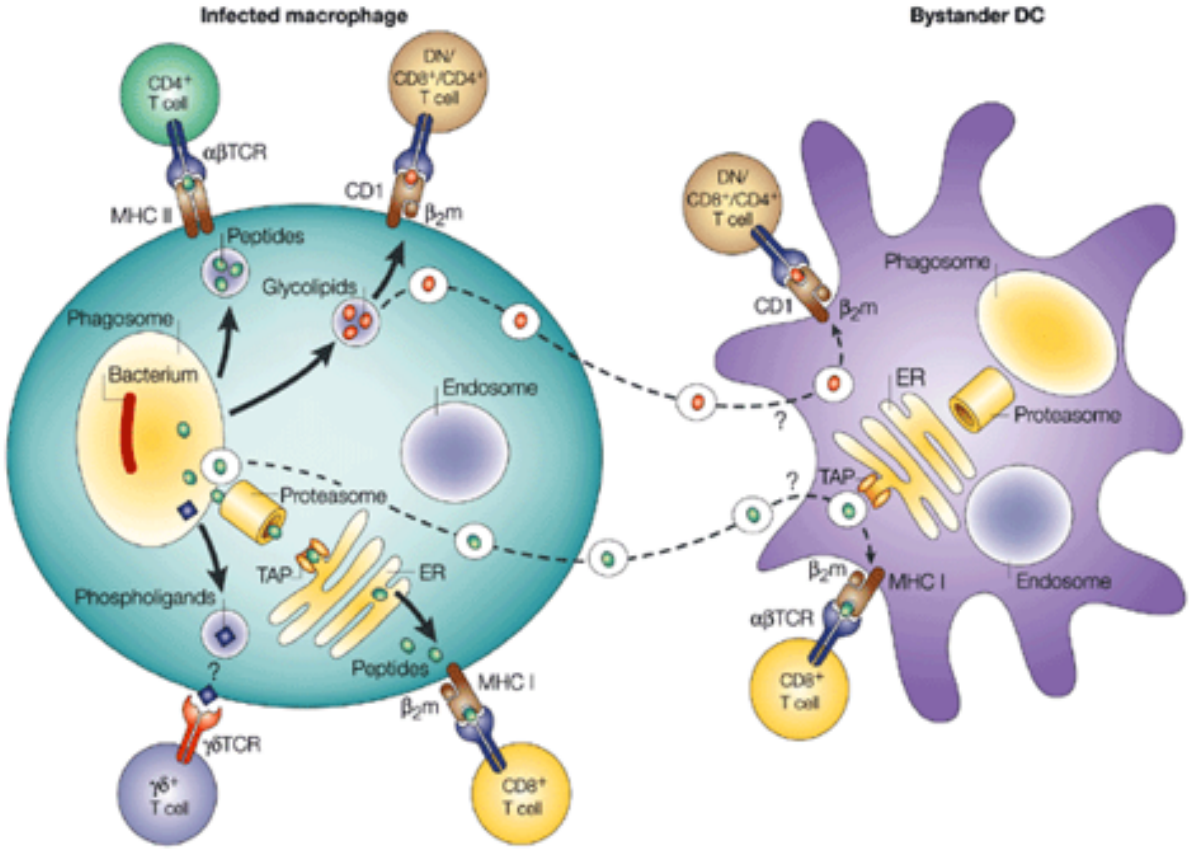


Tuberculin test:

After intradermal injection of PPD measure diameter of induration

after 48 hours


Phagolysosome fusion
Acidification
Iron restriction
RNI
ROI
S-nitrosothiols
dinitrosyl
iron complexes
Nitrogen
dioxide
Hydroxyl and
ferryl radicals
Hydrogen peroxide
Peroxynitrite
Nitric oxide
Superoxide
L-Arginine
Oxygen
Activated infected
macrophage
TNFα
IFN-γ
IFN-γ
IFN-γ
IFN-γ
CD4+
T cell
CD8+
T cell
DN/
CD8+/CD4+
T cell
γδ+
T cell
LT-α3
apoptosis
Perforin
granulysin
Perforin
granulysin
Perforin
granulysin
a Spontaneous
healing (?)
b Acute disease
(Immunocompromised)
Containment (>90%)
c
Granuloma
Reactivation
(<10%)
Dissemination
transmission
Perforin
Granulysin
Infected
macrophage
Nature Reviews | Immunology


Infected macrophage
Bystander DC
CD4+
T cell
αβTCR
MHC II
DN/
CD8+/CD4+
T cell
CD1
β2m
Peptides
Glycolipids
Phagosome
Bacterium
Endosome
Proteasome
TAP
ER
Phospholigands
?
γδTCR
γδ+
T cell
Peptides
MHC I
β2m
CD8+
T cell
DN/
CD8+/CD4+
T cell
CD1
β2m
Phagosome
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