جامعة الملك سعود
King Saud University

Immunology of Tuberculosis

MED438
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Color code:
Important in red
Extra in blue

Immunology
MED438

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Editing file

Objectives

- To know how M. tuberculosis infection is contracted and its initial encounter with the immune system
- To understand the delayed type of hypersensitivity reaction against M. tuberculosis
- To be familiar with the possible outcomes of the infection with M. tuberculosis in immunocompetent and immunocompromised hosts
- To understand the basis of the tuberculin test and its importance in gauging immunity against M. tuberculosis

Introduction to Tuberculosis

- Mycobacterium tuberculosis is the second most common infectious cause of death in adults worldwide, with an increasing incidence due to HIV.
- TB is transmitted through aerosols (airborne transmission) by coughing or sneezing and acquired mainly through inhalation.
- The clinical development of the disease depends solely on the effectiveness of the host's innate and adaptive immune response to the infection. If the immune response is functioning well, the clinical disease has little to no chance of developing.

Tuberculosis is able to withstand the body's immune response after being phagocytosed by several ways, including:

Virulence factors	Host factors
The lipid-rich **Waxy outer coat** blocks phagocytic enzymes.	Resistance to reactive oxygen intermediates.
Catalase-peroxidase resists the host cell oxidative response.	Inhibition of phagosome-lysosome fusion
The glycolipid **Lipoarabinomannan** (LAM) Stimulates cytokines, resists the host oxidative stress and interferes with MHC Class II expression to CD4 cells	Inhibition of phagosome acidification. (prevents digestion in an acidic environment)
	Escape from the phagosomal compartment of the cytoplasmic space

Possible outcomes of TB infection

- Immediate clearance
- Immediate onset (primary)
- Latent
- Onset after many years (Reactivation)

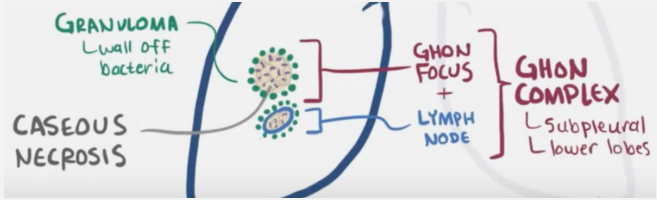
Primary disease

The process of primary TB can be split into the following steps:

1- Inhalation: The bacteria enters the body via inhalation

2- Phagocytosis: The alveolar macrophages phagocytose the bacteria, but cannot kill it

3- Recruitment: The infected macrophages send out a distress signal in the form of chemokines, attracting other macrophages.



4- Ghon's focus: The newly recruited macrophages surround the bacteria, this eventually forms a nodular granuloma called a tubercle. This whole structure is known as a Ghon's focus.

5-Ghon's complex: If the replication isn't controlled, it spreads to the draining lymph nodes, forming a Ghon's complex.

6- Ranke's complex: In some cases, the tubercles become fibrotic and heal, forming a Ranke's complex. This type of fibrosis never goes away.

Primary disease

2-6 weeks after the infection, the bacilli trigger a Cell Mediated Immunity response. This leads to:

01	Th1 cells	**Weeks after the infection, the CMI response causes Th1 cells to release:** • **IFN-ɣ:** activates more macrophages and enhances its ability to kill phagocytosed bacilli • **TNF:** induces local inflammation and activates more macrophages.
02	CMI response	**If the CMI response is not effective, the lung gets destroyed by:** • Nitrogen intermediates • TNF-α • Reactive oxygen • Contents of cytotoxic cells (Perforin, granzymes)
03	Outcome	• The destructive substances lead to caseous necrosis, a major characteristic of TB. • Eventually, the caseating lesions start to erode, spreading to the airways and becoming infectious.
04	Chronic Disease	• If left untreated, the disease can become chronic or even lead to death (80% of cases) • It is characterized by episodes of healing by fibrotic changes around the lesion and tissue breakdown. • Recovery is possible(20%) at this stage, but complete eradication of the bacilli is rare.

Miliary TB

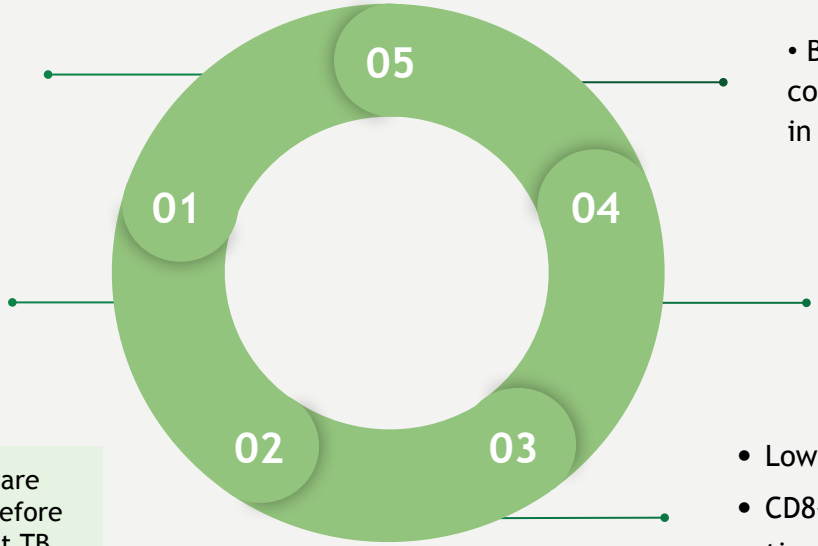
Miliary TB (disseminated TB) can occur if the primary infection is not properly contained. This develops when the TB bacilli spreads throughout the lung and/or to other organs through hematogenous lymphatic spread. Its most common presentation is meningeal TB.

Pathogenesis of Latent TB

- Presentation of antigens by APCs in the lymph nodes.
- Delayed-type hypersensitivity (Type IV).

- Activation of CD4+ (Th1) lymphocytes.
- This phase coincides with high rate of replication of bacilli.

The immune response and Anti-Mtb drugs are directed towards the growing bacilli, therefore making the non-replicating bacilli in latent TB somewhat invisible to the body (resistant).



- Bacterial load remains constant and infection is kept in a dormant state.

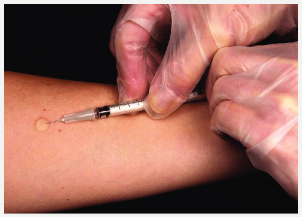
- Induction of high number of CD8+
- Increased production of IFN-γ and cytotoxic activity.
- This phase coincides with bacterial growth stabilization.

- Low induction of CD8+ lymphocytes.
- CD8+ lymphocytes recognize the antigen and produce IFN-γ, leading to macrophage activation.

Reactivation	The dormant bacteria that were stopped during primary infection can start proliferating again (5-10% of cases). It tends to be localized with much less caseation and little lymph node involvement. It usually only affects the lung apices. Dissemination here is usually uncommon.
Factors contributing to reactivation	- Immunosuppression - Malignant Lymphoma - HIV/AIDS - Diabetes - End-stage renal disease - Corticosteroids - Anti TNF-α drugs - Aging

Tuberculosis Tests

1- Mantoux



- It is a delayed-type hypersensitivity(DTH) skin test
- Purified Protein Derivative (PPD) is injected intradermally which causes the area to swell.
- The same area is inspected 2-3 days later and the results depend on the diameter of the induration.
- This response (DTH), however, is not reliable in diagnosis because it cannot distinguish between a reaction from the BCG vaccine and the actual bacteria. Moreover, being immunocompromised can also affect the results of the test.

2- IFN-ɣ release assay

- This test measures the IFN released by T cells when Mycobacterium antigens are injected.
- Early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) antigens are used since they are not found in BCG vaccines.
- If a reaction occurs, this means the body has already been exposed to these antigens prior to this test.
- This helps differentiate between people with latent TB and people who have taken the BCG vaccine, unlike the Mantoux test.

ESAT-6 and CFP-10 are found in the bacteria. So if the bacteria was already in the blood and the antigen was injected, the IFN levels would increase.

Take home messages

- After exposure to M. Tuberculosis, the immune system's handling of the infection determines its final outcome.
- Only a relatively small proportion of individuals develop primary disease.
- Reactivation of tuberculosis can occur in patients who are immunocompromised.
- Tuberculin test should be interpreted with caution, as it may be difficult to differentiate between latent disease and delayed-type hypersensitivity against M. Tuberculosis.

Quiz:

1. M. tuberculosis uses several mechanisms to escape killing by macrophages. Which type of immune cell can help by activating macrophages to enhance killing of intracellular M. tuberculosis?

a) B cells
b) TH1 cells
c) TH2 cells
d) IFN-gamma

2-One cytokine of particular importance in the response to infection with M. tuberculosis is ____Which helps in activating macrophages.

a) IL-12
b) IL-5
c) IFN-ɣ
d) Yez

3. Which one of the virulence factors interferes with MHC class II expression to CD4 Cells?

a) Lipoarabinomannan
b) Waxy outer coat
c) Catalase-peroxidase
d) None of the above

4. When TB gets reactivated, the caseation tends to?

a) Increase
b) Decrease
c) Remains the same
d) Caseation does not occur in TB

5. Which type of immunity plays a major role in fighting TB?

a) Innate immunity
b) Adaptive immunity
c) Both innate and adaptive
d) Humoral immunity

6. A patient came into the clinic and had a mantoux test done. The test came out positive, and the doctor immediately suspected that he was infected with TB. Can the doctor be wrong?

a) No, the mantoux test is a good indicator for TB infection
b) Yes, the mantoux test can give a false positive
c) Yes, an IFN-ɣ release assay has to be done for confirmation
d) Both b&c

1.B 2.C 3.A 4.B 5.C 6.D

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