TB Pathogenesis

What is it?

• One of the oldest recorded human afflictions
• Bone TB from individuals who died 4,000 years ago
• Assyrian clay tablets record hemoptysis 7th century BC
• Hippocrates describes symptoms of consumption from the 5th century BC
• Until mid-1800s, many believed TB was hereditary or a working man's disease

• 1865 Jean Antoine-Villemin proved TB was contagious

• 1882 Robert Koch discovered *M. tuberculosis*, the bacterium that causes TB

**Mycobacterium tuberculosis**

**What is it?**

• Caused by the Mycobacterium *M. tuberculosis*

• Small, aerobic, non-motile bacillus

• High lipid content- lipid bilayer
  - Does not stain well
  - Can live in a dry environment for weeks
  - Can withstand some disinfectants

• Divides at the slow rate of 16-20 hours.

• Can be identified under a regular light microscope.

• Most mycobacterium retain stains even after washes and therefore are called “acid-fast” bacilli or AFB

• Common staining techniques are:
  - Ziehl-Neelsen stain-bright red
  - Auramine-rhodamine stain- fluorescence microscopy
TB Pathogenesis

- TB is spread person to person through the air via droplet nuclei
- *M. tuberculosis* may be expelled when an infectious person:
  - Coughs
  - Sneezes
  - Speaks
  - Sings
- Transmission occurs when another person inhales droplet nuclei

*Mycobacterium tuberculosis*

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**TB Pathogenesis**

**What it does**

1. Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the small alveoli.

2. Tubercle bacilli multiply in alveoli, where infection begins.

3. A small number of tubercle bacilli enter bloodstream and spread throughout body.
**TB Pathogenesis**

**What it does**

- Within 2 to 8 weeks, MTB can be phagocytosed by alveolar immune cells
- The phagocytosed immune cells transport the MTB to local lymph nodes for T cells priming and cloning
- The immune cells form a barrier shell that keeps the bacilli contained and under control (LTBI)

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**TB Pathogenesis**

**What it does**

- If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease
- This process can occur in different places in the body

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**Clinical Disease** *M. tuberculosis* can cause

- Initial infection of *M. tuberculosis* (primary)
- Progressive disease (primary TB)
- Dissemination of MTB
  - Stabilization (healing)
  - Recurrence (reactivation or primary TB)
- Resuscitation
Events following entry of bacilli
TB Pathogenesis

Stage 1:
- Phagocytosis of MTB by Alveolar macrophage
- Destruction of MTB, but some evade destruction & continue to multiply and then infect bystander macrophages

Events following entry of bacilli
TB Pathogenesis
Stage 2:
- Influx of Polymononuclear cells (PMN) and Monocytes-differentiate into Macrophage
- In some cases, it fails to eliminate the bacilli completely
- Logarithmic growth of bacilli-little tissue destruction

Events following entry of bacilli
TB Pathogenesis
Stage 3:
- Antigen specific T-cells are recruited to the site and activate monocytoyid cells and differentiate into two types of Giant cells
  - Epithiliod
  - Langhan
- Infection is walled off from rest of the body which prevents dissemination of bacilli.
Events following entry of bacilli
TB Pathogenesis

Stage 4:
- Stage of Latency (Granuloma) disrupts under conditions of failing immune surveillance & leads to endogenous reactivation of dormant bacilli
- Characterised by caseation necrosis

The Great Tuberculosis Paradox

• Up to 50% of people with close and repeated contact with confirmed index cases, even in high burden areas, have no immunodiagnostic evidence of Tb disease.
  - Sterilizing innate immunity
  - Likely related to host factors
Immunopathogenesis of TB

- Likelihood of transmission of *M. tuberculosis* from index case to a contact person depends on:
  - Intensity of exposure
  - Exposure duration
  - Sputum related host factors
  - *M. tuberculosis* strain virulence

TB Immunopathogenesis

- **Immune system vs. MTB**
  - Local inflammation
  - Activation of α/β T cells
  - Enhanced cytokine response
  - A lot of IFN-γ released

- **MTB immune evasion techniques**
  - Suppressive cytokines (TGFβ)
  - Effector molecules
  - Treg cells

TB Immunopathogenesis

- **The Achilles heel**
  - Increased susceptibility to TB with:
    - Suppressed CD4 or CD8 T cell levels - HIV
    - TNFα blockage
    - Hereditary IFN-γ
    - IL-2 receptor abnormalities or inhibition
  - Insight into immune requirements for protection against MTB
**Innate Immunity to *M. tuberculosis***

- Promote bacterial killing with phagosomal maturation, producing reactive nitrogen and oxygen intermediates.
- Several pathways and cell types mediate an innate immune response to MTB.
- Therefore, many individuals may fail to have an immunodiagnostic evidence of MTB infection despite prolonged or high-risk exposure.

**Adaptive Immunity to *M. tuberculosis***

- Mycobacterial infected macrophages and dendritic cells present antigens to T cells and B cells.
- Macrophage apoptosis releases apoptotic vesicles with MTB to uninfected DC for even greater antigen presentation.
Adaptive Immunity
CD4 T cell

- Th1
  - INFγ, TNFα, IL2, GM-CSF
  - Stimulation of CTL, macrophage activation
- Th2
  - IL4, IL5, IL10, IL13
  - B cell stimulation
  - Suppress Th1
- Th17
  - IL17, IL17F, IL21, IL22
  - Defesin, recruit neutrophils and monocytes
- T reg
  - TGFβ
  - Modulate T cell response

Adaptive Immunity to *M. tuberculosis*

- Activates and recruits immune cells
- Kills mycobacteria-infected cells

Adaptive Immunity to *M. tuberculosis*

- B cells were not thought to have a significant role in protecting against MTB
- Recent work showed that B cells were needed in MTB infected mice by acting as an intermediary for cellular immunity and the complement pathway.
Adaptive Immunity to *M. tuberculosis*

- Memory T cells are created specific to MTB antigens.
- Memory T cells are active and proliferate with recall responses.
- Specific, practical, clinical biomarkers of protective immunity has not been established.

Histology of TB disease

- Delayed hypersensitivity reaction
- Central Caesating necrosis
- Surrounded by lymphocytes, multi-nucleate giant cells and epitheloid macrophages
- Organisms may be identified within the macrophages.
Immunomodulation for Cure of TB

- Improve sterilizing immunity
- Decrease collateral damage of the immune system

- 95% of bacterial sterilization occurs in 2 weeks, but 6 months of therapy is needed.
  - Is immune modulation needed to stop a destructive immune pattern to a protective one?

Immunomodulation for Cure of TB

- Drive a Th1 response, turn off T reg
  - IL2, INFγ, steroids, thalidomide, TNFα antagonist-failed!
  - IVIG dramatically improves mycobacterial sterilization in a mouse model

- Many other agents in different stages of discovery and clinical trials

M. Tuberculosis vaccines

- MTB antigens ESAT-6, CFP-10 Ag85
  - Found in latently infected, or exposure individuals
  - Induce cytokine specific immune response
  - Provide protective immunity in animal models

- Provide a protective antigen through a vaccine or viral vector/gene therapy
M. Tuberculosis vaccines
Bacille Calmette Guerin

- BCG protective effect
  - Age, background infection rates, virulence of MTB strain, co-infection with helminths, T cell immunity to helminths, malnutrition
  - All factors that module the immune system
- Protects against MTB dissemination
- May protect against adult MTB infection in household contacts
- Prevent primary infection and/or prevent transition from LTBI to infection

Vaccine Candidates for MTB

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Description</th>
<th>Stage</th>
<th>Sponsor(s)</th>
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<td>tAg with adjuvant containing 6 antigens</td>
<td>Phase 1</td>
<td>ULS, Intrametals</td>
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<td>OPIVA</td>
<td>HLA-A2 restricted fusion protein</td>
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<td>NewPath/PATH/IHR</td>
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<td>N94</td>
<td>Asr 4 fusion antigen</td>
<td>Phase 1</td>
<td>GSK/Pasteur</td>
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</tbody>
</table>

Challenges in vaccine development

- Children and adolescence
- HIV/TB co-infection – poor T cell response
- HIV/Helminth co-infection- strong Th2 response
- No good functional immune assays to predict a sterilizing response
- Role of Aerosolized vaccination?
TB Pathogenesis

Immunopathogenesis!

La Miseria by Cristobal Rojas (1886).