Mycobacterium tuberculosis
Transmission and Disease Progression

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Centers for Disease Control and Prevention

TB Intensive Workshop
Newark, NJ
April 12, 2011
Objectives

- Understand transmission dynamics
- Review TB immunology and pathogenesis
- Demonstrate public health implications
  - Vaccination and therapeutics
  - Diagnostics
Route of Transmission

[Diagram showing the transmission route with text: 10-15 individuals infected per minute]
Transmission of Tuberculosis

Transmission

Primary Tuberculosis

Latent Tuberculosis

“Reactivation” Tuberculosis

Skin-test conversion in 6 to 8 weeks

Spontaneous healing in 6 months

Progression after 2 years, 5%

Progression within 2 years, 5%

Progression with concurrent HIV infection, 10% each year

Probability of Transmission

- **Host**
  - Inoculum (smear, culture, cavitation)
- **Organism**
  - Virulence factors
- **Environment**
  - Space/ventilation
  - Time
Variations in Inoculum

- **Estimates of** *M. tuberculosis* **aerosol production (quanta per hour)**
  - Patient on early treatment ~1
  - Untreated cavitary TB 13
  - Laryngeal TB 60
  - Bronchoscopy 250

Fennelly KP. Int J Tuberc Lung Dis 1998; 2: S103
Environment
TB Outbreaks Move Through Time

- **Imprisoned**
  - TST negative

- **Clinic Visits #1–4**
  - Cough, wheezes

- **Clinic Visit #5**
  - Cough, CXR abnl, No action taken

- **Hospitalized with Pulmonary TB**
  - Released from prison

- **Clinic Visit #6–7**
  - Cough, CXR abnl, No action taken

TB Moves Through Place

Key

- Location
- Source patient
- Secondary patients

Friend’s Home → Correctional Facility → Friend’s Home → Cousins’ Home → Cousins’ Home → TB Diagnosis

Feb–May → May – Jan → Jan → Jan–Mar → Mar–May

S H → S B G → S D → S B C F E → S B F

TB Moves Through Place
TB Can Appear as Outbreaks
Amplifiers of TB Transmission

- Soup Kitchen
- Shelter
- Homeless Clinic
- Jail
- Detention Center
- Hospital ED
- BAR (drinking glasses)
TB Genotyping Program

- Spoligotyping
- Mycobacterial interspersed repetitive units (MIRU)
Mycobacterium tuberculosis

- Obligate aerobes
- Slow-growing
- Intracellular pathogens
- Hydrophobic: lipid content in the cell wall
- LAM (lipoglycan lipoarabinomannan)
- “Acid-fast bacilli”

Acid Fast Bacilli

carbolfuchin stain

fluorochrome stain
Pathogenesis

- Outcome from infection depends on immune responses
- Certain medical conditions increase risk for progression to TB disease
Conditions Increasing Likelihood of Progression from Infection to Disease

- Very young age
- T-cell deficiency (e.g., HIV)
- Treatment with TNF-alpha antagonists
- Solid organ transplantation
- High-dose corticosteroids
- Diabetes mellitus
- End-stage renal disease
- Malnutrition
- Silicosis
- Hypercholesterolemia?
Natural History of TB Infection

- **Acute**
  - 1 progressive disease (<5%)

- **Chronic**
  - Reactivation disease (5%)
  - Persistent infection (90%)

Adapted from: Dr. Henry Boom, Case Western Reserve University
Antimycobacterial Immunity

**Innate Immunity**
- Cell populations (Toll-like receptors)
- Bactericidal molecules
  - Enzymes (lysozyme, etc.)
  - Reactive nitrogen and oxygen intermediaries

**Humoral Immunity**

**Adaptive Immunity**
- Cell-mediated Immunity
- Phagocytes (Antigen presenting cells)
  - Macrophage
  - Dendritic
  - Monocytes
- Effector cells
  - CD4+, CD8+ T cells
  - CD1 (NKT)
  - γδ T cells
- Cytokines (IFN-γ, TNF-α, IL-12, IL-4)
To l l-like Receptors (TLRs)

- TLRs initiate first immune response
- TLR-8 on the X chromosome
- Males have 1 copy - may be more susceptible
First line of defense

- Dendritic cells
- Macrophages
- Stimulated T cells
Microscopic Level
CD4+ / Human Leukocyte Antigen Interaction
Cellular Immune Response
Cytokine Storm
Host Responses

8 – 9 days post-infection

Dendritic cells sampling the mucosal airway respond rapidly to pathogen signals and migrate to the draining lymph node.

Once bacteria arrive in the draining lymph node, naive T cells are activated, proliferate, and become effector cells.

Dendritic cells sampling the alveolar tissue do not respond rapidly to pathogen signals; mycobacteria are not rapidly transported to the draining lymph node.

Availability of specific cytokines will define the phenotype of the effector T cells.

Effector T cells migrate from the lymph node through circulation and are attracted to the lung tissue by inflammation.

18 – 20 days post-infection

Antigen-specific effector T cells remain in the inflammatory lesion and mediate protection.

Cooper AM. Annu Rev Immunol 2009 27:393
Granuloma
When Host Immunity Fails

- Mycobacteria are spread by migrating cells to local lymph nodes
- From the lymph nodes, they disseminate via the bloodstream to different body sites
- They may continue to grow and cause early disease at any site
- They may be contained, then “reactivate”, especially in the lung apices, but anywhere is possible
**M. tb Strategies to Evade Host Immunity**

- **Cell membrane**
  - Fatty acids
  - NO arginase inhibition
  - Efflux pumps
  - Mannose coating

- **Resistance to phagosome pH**

- **CD4 cells remain compartmentalized unable to be mobilized to lymph nodes**

Evasion of Acidic Conditions

Inhibition of

- Phagosome-lysosome fusion
- Lysosome acidification
- Activation of hydrolytic enzymes
Role of Efflux Pumps

Public health implications
The usefulness of urine-LAM (lipoglycan lipoarabinomannan) is limited because of low sensitivity. Sputum-LAM has better sensitivity but poor specificity.

Priming the Immune System: Bacille Calmette-Guérin (BCG) Vaccine

- Calmette & Guérin 1908-1921
- No new TB vaccine in 90 years
Potential Uses of a TB Vaccine

Block Initial Infection

Prevent Early Disease

Prevent Latent Infection

Prevent Reactivation
Vaccine Development

- **Live attenuated vaccines**
  - Genetically-modified BCG
  - Genetically engineered mutants
  - Live attenuated vectors (viruses or bacteria)

- **Subunit vaccines**
  - Protein, peptide, lipid, or carbohydrate antigens, with or without adjuvants

- **DNA vaccines**
  - DNA encoding whole proteins or peptide epitopes of *M. tuberculosis*
### TB Vaccine Pipeline

<table>
<thead>
<tr>
<th>Vaccine Candidate</th>
<th>Pre-Clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIb</th>
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Clinical trials with MVA85A

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<td>2005</td>
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<td>Phase IIb (HIV-infected Adults - multisite TB021)</td>
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Helen McShane. Jenner Institute, University of Oxford. 2010.
Implications for Therapy

- Immune modulation
  - Use of IFN-α as an immune modulator
  - *Ex vivo* pulsing of dendritic cells to prime T cells

- Target specific sites
  - Receptors
  - Efflux pump
  - Genes
Clinical Correlate

- Tumor necrosis factor (TNF)-α
  - Maintain granuloma compartmentalization
  - Factor in pathogenesis of RA
- TNF blockers reactivate LTBI

MMWR 2004; 53(30): 683-686
TST Versus In-vitro Assays

Presentation of mycobacterial antigens

Antigen presenting cell

Memory T cell

Skin test

in-vitro blood test

Measurement of induration

IFN-γ

TNF-α

IL-8, etc

Measurement of IFN-γ production

IFN-γ

TNF-α

IL-8, etc

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T cell-Based Diagnostics
IFN-gamma Release Assays (IGRA’s)

- IFN-g is a pro-inflammatory cytokine released by T cells and NK cells
- Two commercially available tests:
  - QuantiFERON® TB Gold IT
  - T-Spot® TB
Tuberculin skin test
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<td>Anergy Recent Infants</td>
<td>HIV infected &lt; 10 weeks Age &lt; 6 mos</td>
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Summary

- *M. tb* is an intracellular organism with several virulence and defense mechanisms
- Host response is mediated especially by the T helper
- Knowing host/organism interactions is useful for developing diagnostic tests and treatment modalities including vaccines
Thank you!