



Center for Tuberculosis

TUBERCULOSIS CLINICAL INTENSIVE



OCTOBER 6-8, 2026 | ROCHESTER, MINNESOTA | SIEBENS BUILDING | LEIGHTON AUDITORIUM

Pathogenesis of Tuberculosis

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Accreditation Statement



Accreditation Statement

In support of improving patient care, Mayo Clinic College of Medicine and Science is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

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UAN Number: UAN JA0000238-0000-26-089-L99-P.

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This activity was planned by and for the healthcare team, and learners will receive 18.25 Interprofessional Continuing Education (IPCE) credit for learning and change.

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A record of attendance will be provided to all registrants for requesting credits in accordance with state nursing boards, specialty societies or other professional associations.

For disclosure information regarding Mayo Clinic School of Continuous Professional Development accreditation review committee member(s) and staff, please go here to the course accreditation page.

Available Credit

- 18.25 ACPE,
- 18.25 *AMA PRA Category 1 Credit™*
- 18.25 ANCC
- 18.25 Attendance
- 18.25 IPCE

Disclosures

NO RELEVANT FINANCIAL CONFLICTS OF INTEREST TO
DISCLOSE

Learning Objectives

Describe the natural history of tuberculosis

Describe the components of MTB and the host immune system important for the pathogenesis of TB

Have a general understanding of the bacteria host interaction in TB

IT'S NOT SIMPLY

"Germ gets in, person gets sick."

Exposure $\neq$ Infection

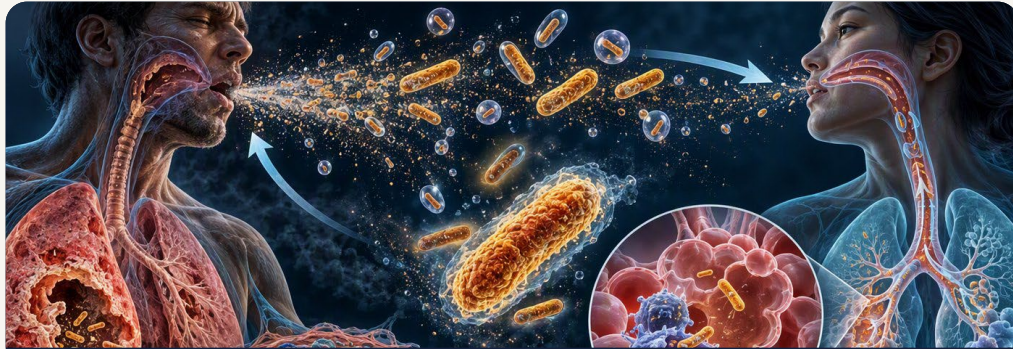
Infection $\neq$ Disease

PART 1 OF 3

The natural history of untreated TB

PART 1 • THE NATURAL HISTORY

How people acquire TB



Dominant route

Airborne inhalation

Droplet nuclei from a person with pulmonary or laryngeal TB reach the alveoli, where alveolar macrophages meet the bacillus.

UNCOMMON ROUTES

Ingestion

M. bovis in unpasteurized dairy; GI entry

Zoonotic contact

M. bovis from infected animals; occupational

Congenital / perinatal

Placental spread, or infected fluids at birth

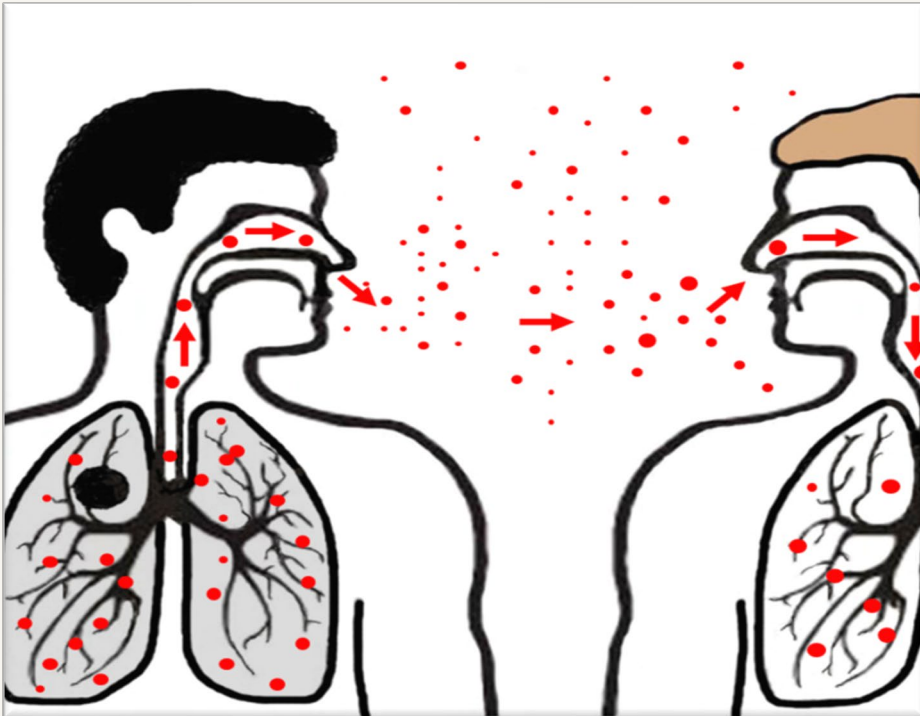
Skin inoculation

Lab, autopsy or instrument injuries

Iatrogenic

Donor-derived TB after transplant

Factors affecting transmission



Susceptibility of exposed person

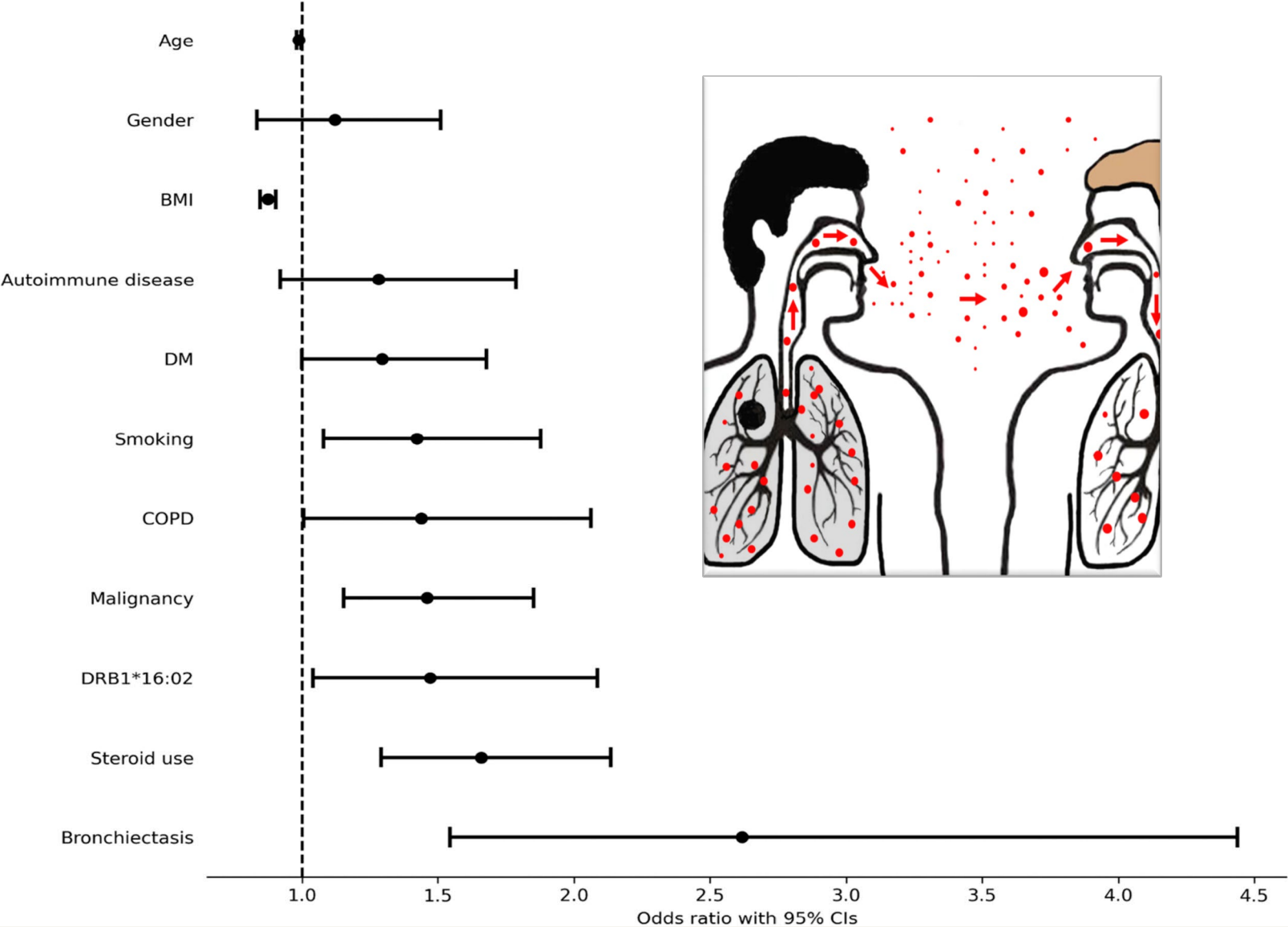
Infectiousness of patient

- Cavitation
- Smear positive
- Laryngeal

Environment

- Small enclosed spaces
- Poor ventilation

Proximity, frequency and duration of exposure



PART 1 • THE NATURAL HISTORY

100 household contacts. What happens to them?

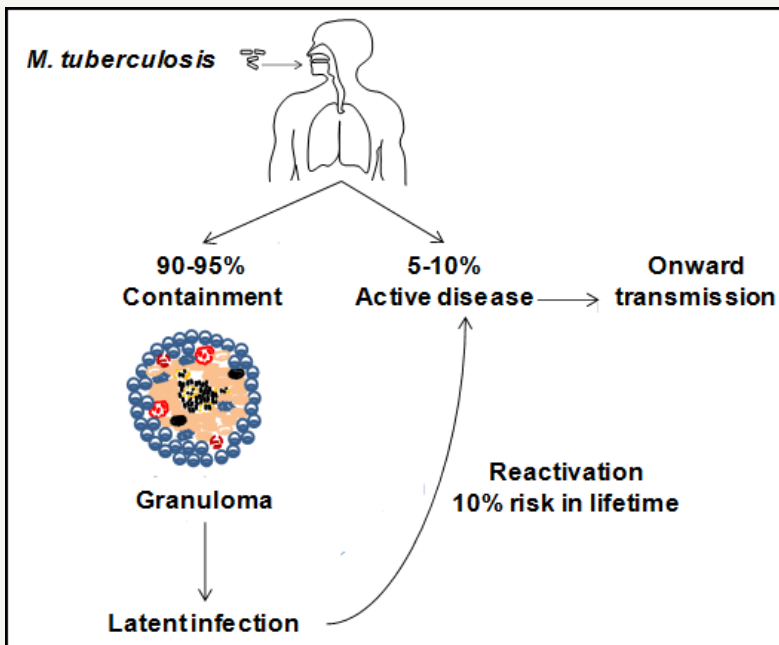
One person with pulmonary TB
coughing in a shared home

Never infected

Infected, then cleared or controlled for life

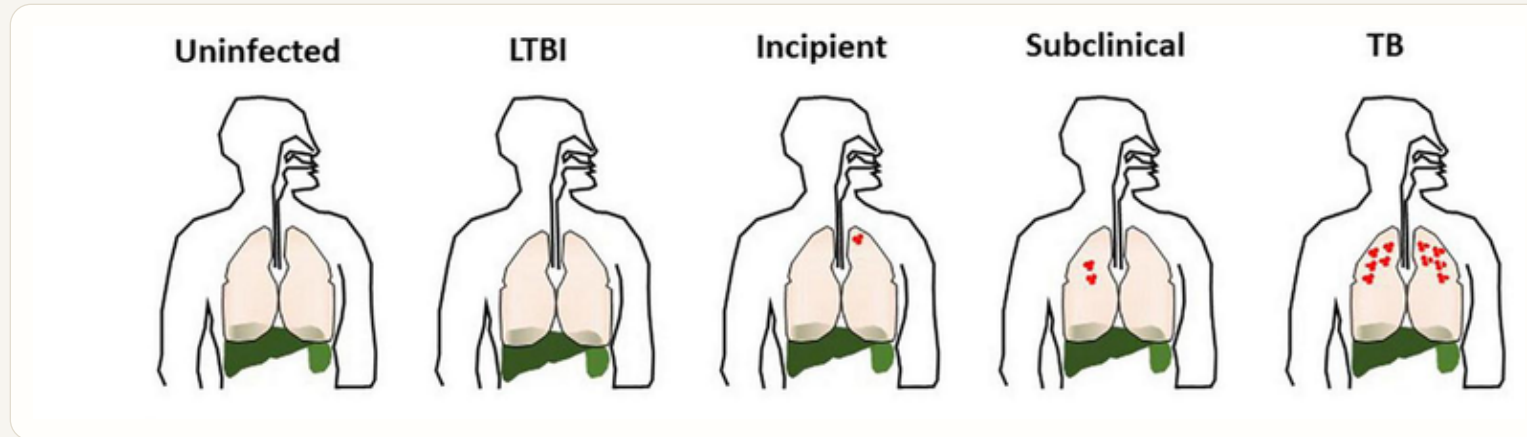
Disease soon: within months to ~2 years

Disease late: years or decades later



PART 1 • THE NATURAL HISTORY

Infection and disease form a spectrum



Incipient TB

Viable *M. tuberculosis* that is likely to progress to active disease in the absence of intervention, but with **no symptoms, no radiographic abnormalities, and no microbiologic evidence**

Subclinical TB

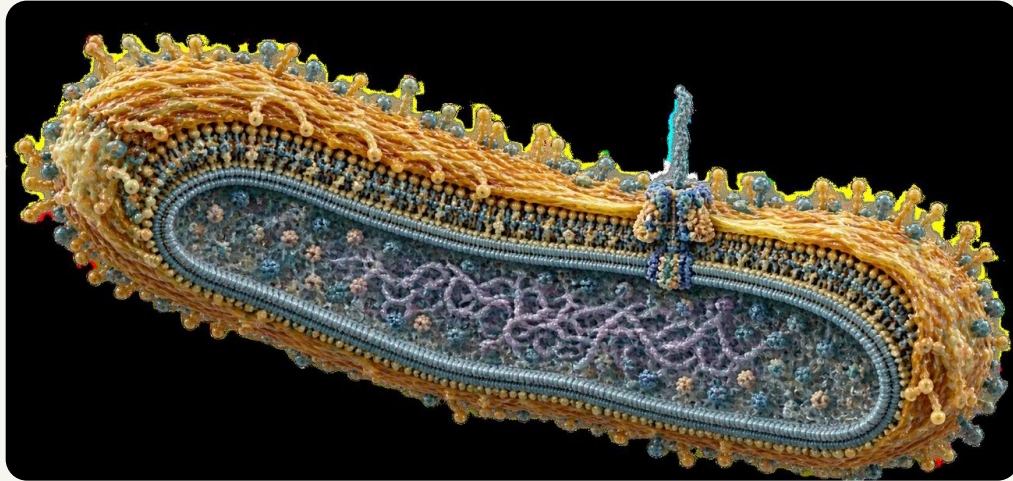
Viable *M. tuberculosis* that does not cause recognized TB symptoms but produces **detectable abnormalities on existing radiologic or microbiologic assays**

PART 2 OF 3

The dynamic duo

PART 2 • THE BACTERIUM

M. tuberculosis



A side note: ESAT-6 and CFP-10 are the antigens the IGRA measures. BCG lacks them, so BCG does not cause a false-positive IGRA.

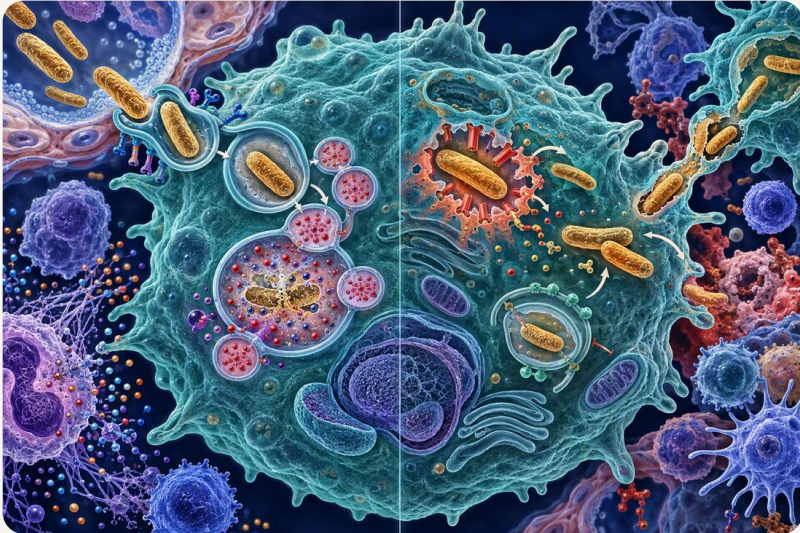
Gets in. Tiny droplet nuclei reach the alveoli; a few bacilli suffice

Survives. Waxy, lipid-rich wall (mycolic acids, cord factor, PDIM); physical/chemical barrier, immune evasion

Escapes and spreads. ESX-1 secretes ESAT-6/CFP-10, breaching the phagosome

Slow growth. (~20 h doubling); dormant, evade immune recognition and survive within macrophages, resistance

The first responders



The body's rapid, built-in defense, present from birth and active within minutes to hours of an infection.

Barriers

Mucus and the mucociliary escalator clear most inhaled particles

Alveolar macrophages

First to meet the bacillus. Resident immune cells continuously patrol the alveolar spaces.

Recruited cells

Neutrophils, dendritic cells, NK cells; dendritic cells carry antigen to nodes

TLRs

Detect the bacillus and trigger cytokines (acting as bridge between Innate and adaptive)

PART 2 • THE HOST: ADAPTIVE IMMUNITY

The specialists, and the granuloma

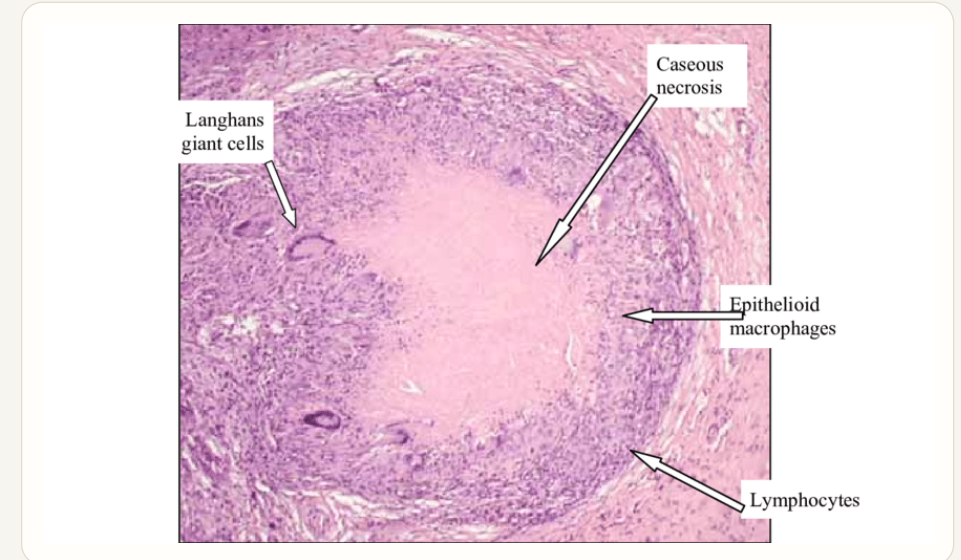
Dendritic cells carry antigen to lymph nodes and prime T cells. This takes weeks.

CD4 Th1 cells release IFN- γ , which activates macrophages to kill. This is the cornerstone of adaptive anti-TB immunity.

CD8 T cells kill infected cells; **Th17 cells** help recruit other cells.

B cells and antibodies play a real but still-unsettled role.

Granuloma: the pathologic hallmark of M. tuberculosis infection.



A granuloma on histology: a caseous core ringed by epithelioid macrophages, Langhans giant cells and lymphocytes.

PART 3 OF 3

Why it happens

The natural history, replayed as a contest between the dynamic duo

PART 3 • EXPOSURE

Why exposure doesn't always lead to infection

Bacterium

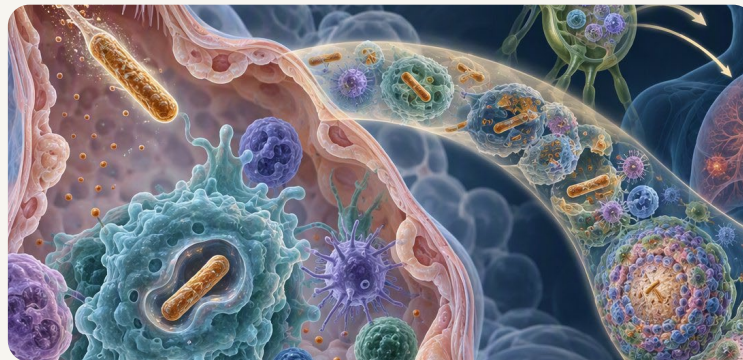
Needs a droplet nucleus small enough to reach an alveolus, and a large enough dose

Host

Mucus and cilia trap and clear most inhaled particles before they arrive

Host

Some alveolar macrophages kill the bacillus outright: early clearance, often with no lasting memory, so tests stay negative



20–25% of exposed individuals appear to clear *M. tuberculosis* before an adaptive response develops and never convert their IGRA/TST

Phagocytosis: Trying to Kill the Bacteria

Recognition and Binding

- Pattern Recognition Receptors, PRRs, on macrophage bind to Mtb surface molecules

Engulfment

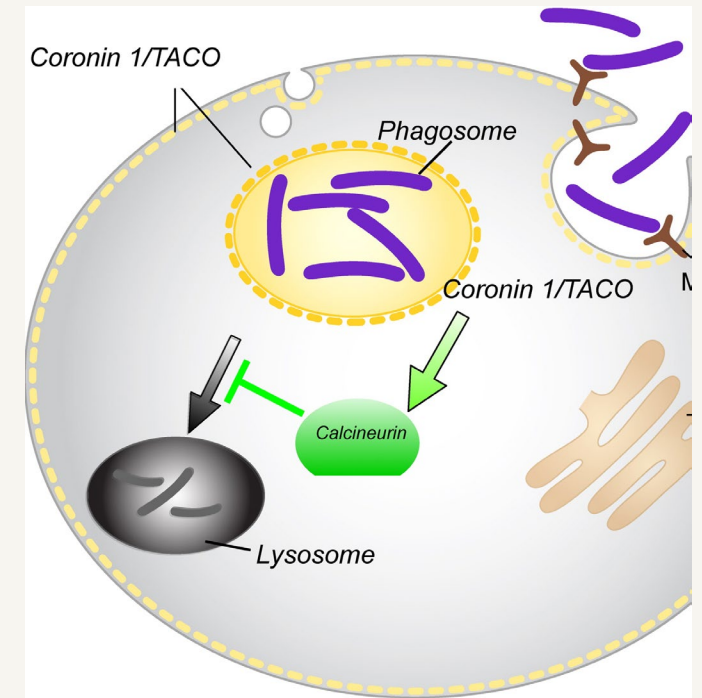
- Macrophage membrane extends around bacterium, forming a phagosome (membrane-bound compartment)

Phagosome Maturation

- Phagosome acidifies (pH drops from ~6.5 to ~4.5-5.0)
- Phagosome fuses with lysosomes → phagolysosome
- Highly toxic environment created

Killing and Degradation

- Bacteria killed by toxic compounds and enzymes
- Bacterial components processed for antigen presentation



PART 3 • EVADING INNATE IMMUNITY

Why infection takes hold: the bacterium's head start

Bacterium

- Uses host lipids for nutrition
- Blocks phagosome maturation
- Resists acidification
- Neutralizes oxidative stress

Bacterium

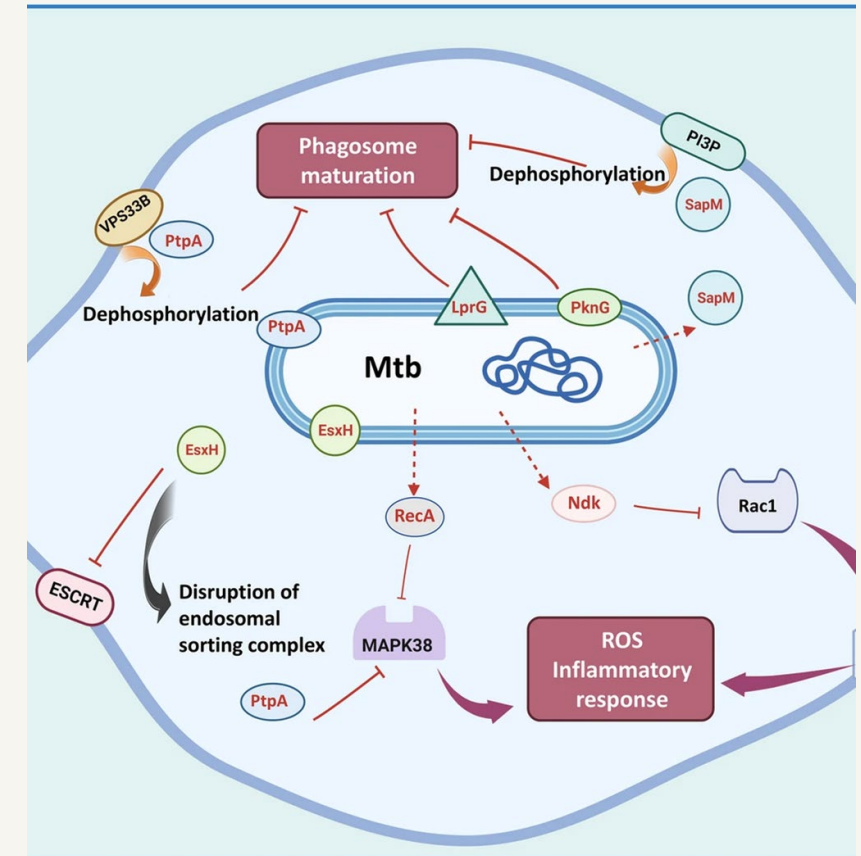
- Delays dendritic-cell migration to the draining lymph node
- Delayed T-cell priming

Bacterium

- Uses ESAT-6 secretion system-1 (ESX-1) to escape and spread into lung tissue (phagosomal rupture, cell-cell spread) infecting newly recruited cells

Bacterium

- Before immunity arrives, it reaches hilar nodes and blood, seeding the apices and distant organs



Adaptive Immunity Against TB and How M. tuberculosis Evades It

Protective adaptive responses are countered at priming, recognition, and effector stages.

Adaptive player (function)	MTB evasion mechanism
CD4⁺ Th1 cells	Delays DC priming; downregulates priming antigens (Ag85B, TB10.4); keeps CD4 ⁺ cells peripheral in granuloma
IFN- γ /TNF drive macrophage killing; organize granuloma	
CD8⁺ cytotoxic T cells	Poor recognition of infected cells; MHC-I downregulation; chronic antigen $\rightarrow$ exhaustion
Kill infected cells; synergize with CD4 ⁺	
IFN-γ	Lipoarabinomannan/lipoglycans blunt TCR signaling; PDIM suppresses CD86/IL-12
Th1 effector cytokine; boosts macrophage autophagy/phagosome killing	
Antigen presentation (MHC-II/APC)	Phagosome-maturation arrest; EsxH blocks ESCRT; Hip1 degrades GroEL2; PE_PGRS47 blocks autophagy
Displays MTB peptides to prime T cells	
Dendritic cells	Delayed DC migration; impaired maturation; $\uparrow$ IL-10/tolerogenic, $\downarrow$ IL-12
Carry antigen to node; prime naïve T cells	
B cells / antibodies	Role less established; surface glycolipids/PGL mask epitopes
Humoral support; BALT near granulomas aids protection	
Regulatory balance (Treg/IL-10/TGF-β)	Exploited: $\uparrow$ IL-10, TGF- β , IDO suppress Th1 and CD8 ⁺ lysis

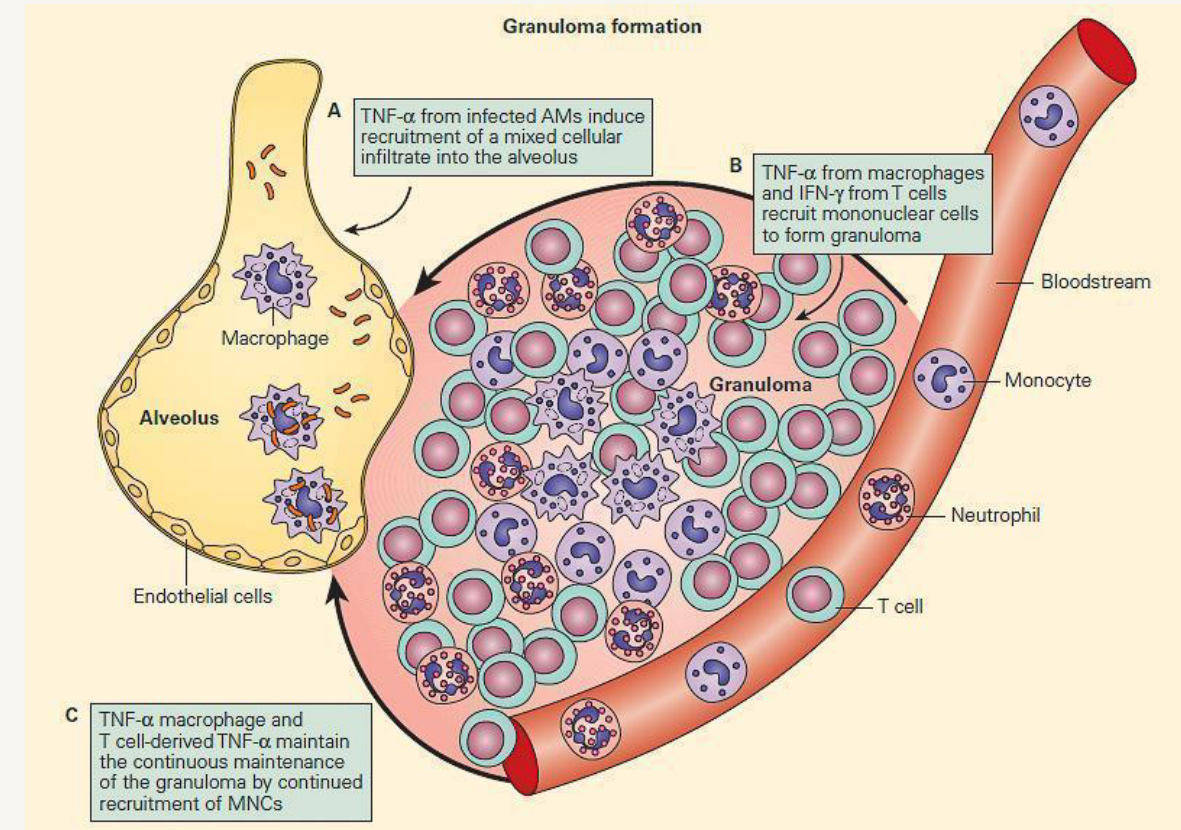
PART 3 • TB INFECTION

The standoff: the granuloma contains and shelters

Host

IFN- γ activates macrophages and TNF organizes the granuloma

Survivors are walled off in low oxygen and switch to a dormant state



Increased Risk for Progression to TB Disease

HIV-infected persons
Diabetes mellitus
Biologics
Transplantation

Those with a history
of prior, untreated TB
or fibrotic lesions on
chest radiograph

Children ≤ 5 years with
a positive skin test for
latent tuberculosis

Underweight or
malnourished persons

Substance users (such
as smoking, alcohol, or
injection drug use)

Certain medical conditions

- Silicosis
- Chronic renal failure/hemodialysis
- Carcinoma of head or neck
- Gastrectomy or jejunioileal bypass

PART 3 • REPLAY: PROGRESSION

Tipping the balance: risk factors map to immunity

Risk factor	What it weakens
HIV	CD4 T cells
TNF inhibitors	TNF, so the granuloma loosens
Infancy, early childhood	Immature innate and T-cell responses
Diabetes, malnutrition, ESRD	Macrophage and T-cell function
Steroids, transplant drugs	T-cell and macrophage activation
Silicosis, smoking	Alveolar macrophage function
Recent infection	The standoff hasn't settled yet

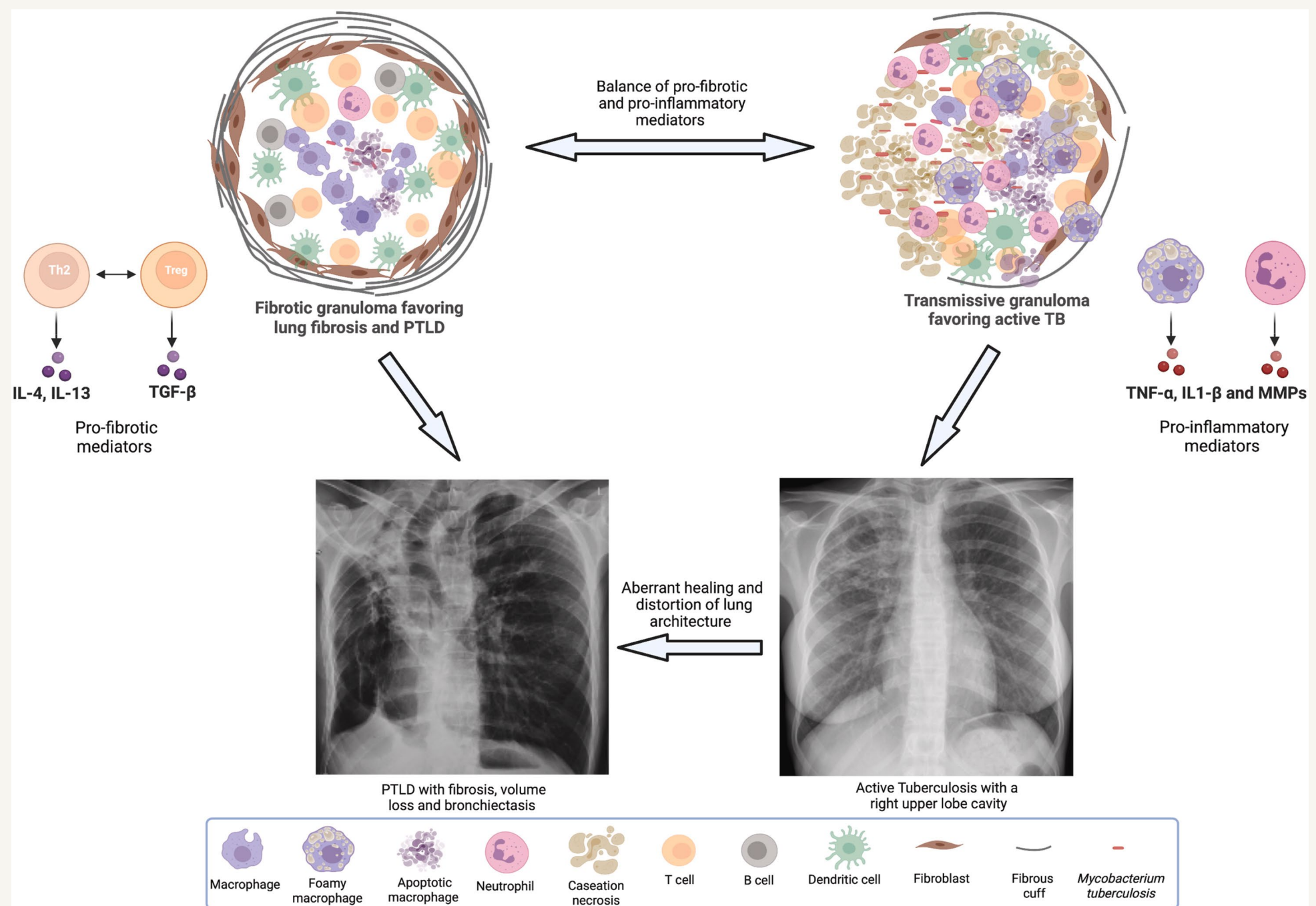
Sources: Lewinsohn 2017 (ATS/IDSA/CDC); Getahun 2015 (NEJM); Bloom 2023 (J Exp Med)

Two Pathways to Tissue/Organ Damage?



Excessive
inflammation

Fibrosis and
scarring



Excessive Inflammation

Key Inflammatory Mediators

TNF- α : Essential for granulomas, but causes tissue necrosis

IFN- γ : Activates macrophages $\rightarrow$ releases toxic enzymes

IL-1 β , IL-6: Drive systemic inflammation

Matrix metalloproteinases (MMPs): Degrade extracellular matrix

Reactive oxygen/nitrogen species: Damage lipids, proteins, DNA

Cellular Contributors

Activated macrophages release degradative enzymes

Neutrophils release proteases and oxidants

CD8+ T cells cause direct cytotoxicity

Dying immune cells release intracellular contents

IT'S NOT SIMPLY

"Germ gets in, person gets sick."

Exposure $\neq$ Infection

Infection $\neq$ Disease



Thank you