Immunity and Immunopathogenesis of TB

Ed Chan, M.D.
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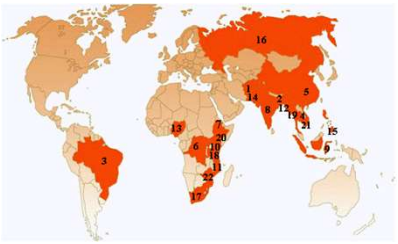
Chane@NJHealth.org

Objective: to better understand the host risk factors for TB

Denver TB Course
No conflicts of interest

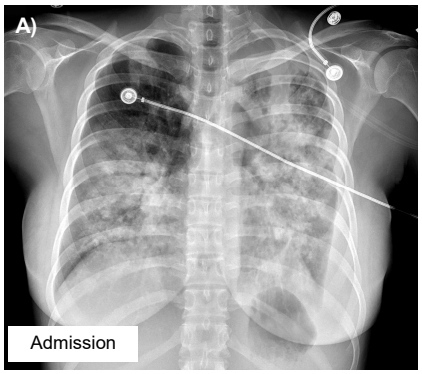
To combat TB, *"follow the middle path."*
Buddha

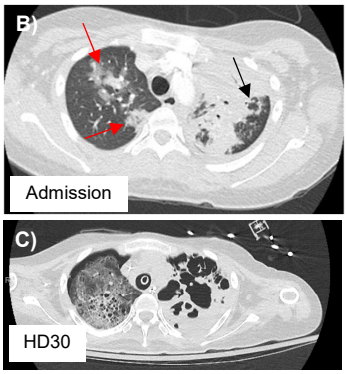
The 22 countries shown on the map accounts for 80% of the TB cases in the world



19 y.o. previously healthy woman with fulminant pulmonary TB

- Presented with 3 days of fever, cough, CP, and dyspnea
- PMH: Three weeks post-partum
- SH: emigrated from the Marshall Islands at age 8
- 101.3^{o}F, 121, 108/60, 42, 85% RA, BMI 20 kg/m^2





Question: Which of the following contributed to TB in this previously healthy young woman?

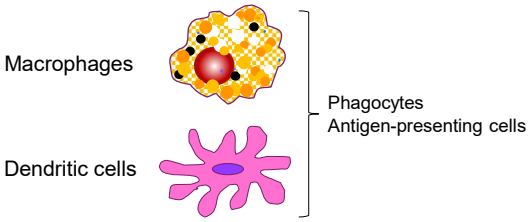
A. Emigrated from the Marshall Islands
B. Post-partum period
C. Thin body habitus
D. Polynesian race
E. The Compact of Free Association Act of 1985 between the U.S. and the Marshall Islands.

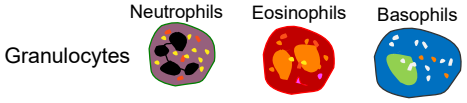
Answer: Yes for A, B, C, and E; maybe for D.

- Marshallese can travel freely to and from the U.S. as non-immigrants without visas; thus, the Marshallese do NOT require screening for active TB or LTBI.
- Between 1946 and 1958, the United States conducted > 50 nuclear tests in and around the Marshall Islands.

Two main arms of the immune system

Innate immunity
"defensive line-man"





Innate lymphoid cells (ILC):
can kill virally-infected cells
• Natural killer (NK) cells
• ILC1/2/3

Adaptive immunity
"line-backers & secondary"

T cells

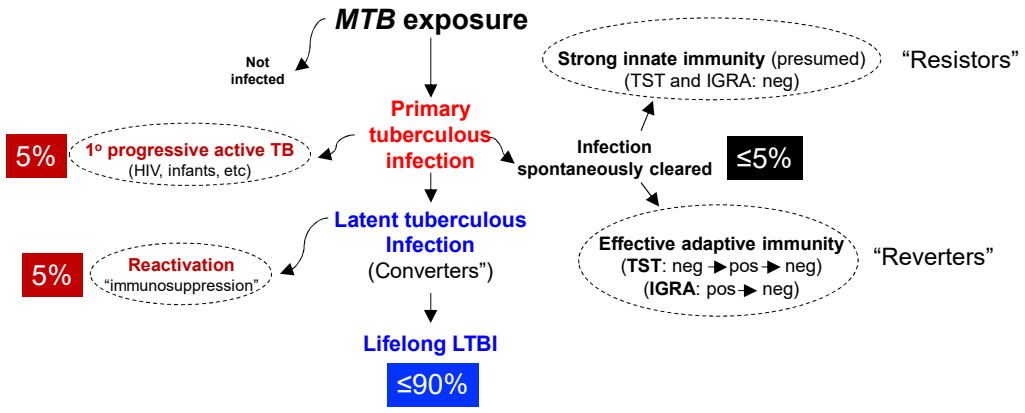
B cells

transitional, naïve, plasma, memory, aged B cells

Mucosal immunity
"coaching staff"

Epithelial cells

Most individuals infected with *MTB* do *not* develop active disease



Ewer K et al. Am J Respir Dis 2006
Elkington PT and Friedland JS. Lancer Infect Dis 2015

Innate Immunity

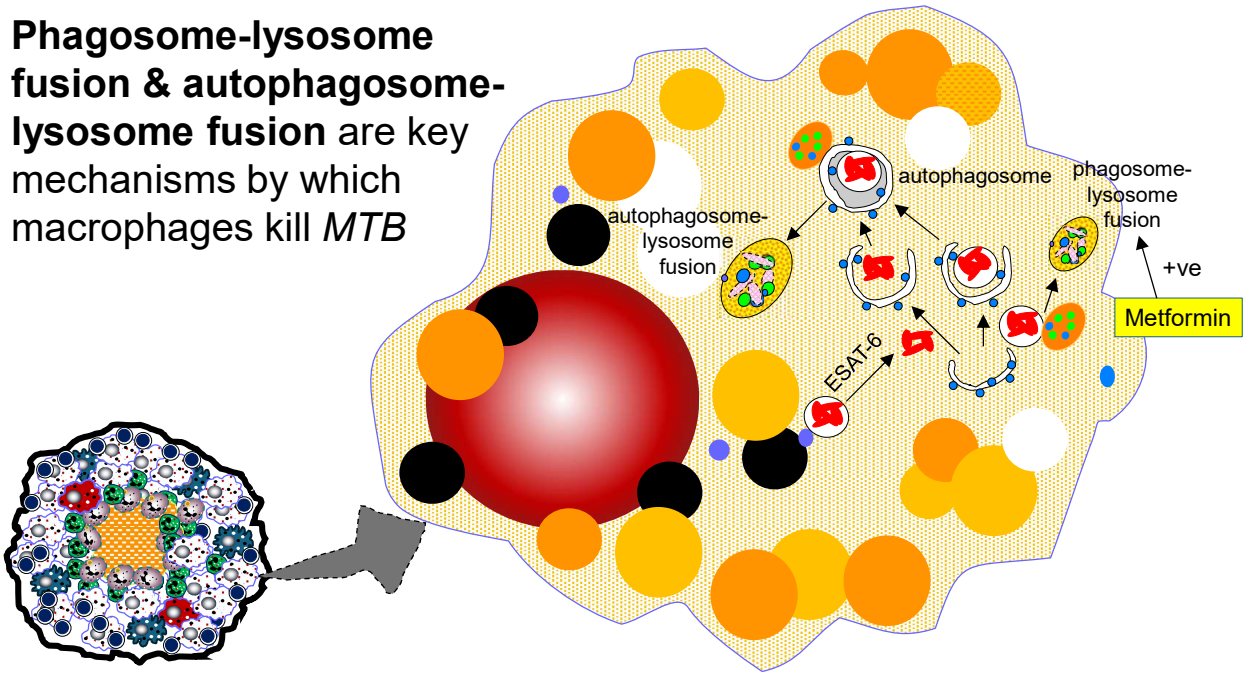
Adaptive Immunity

Spectrum of TB infection and disease in exposed individuals

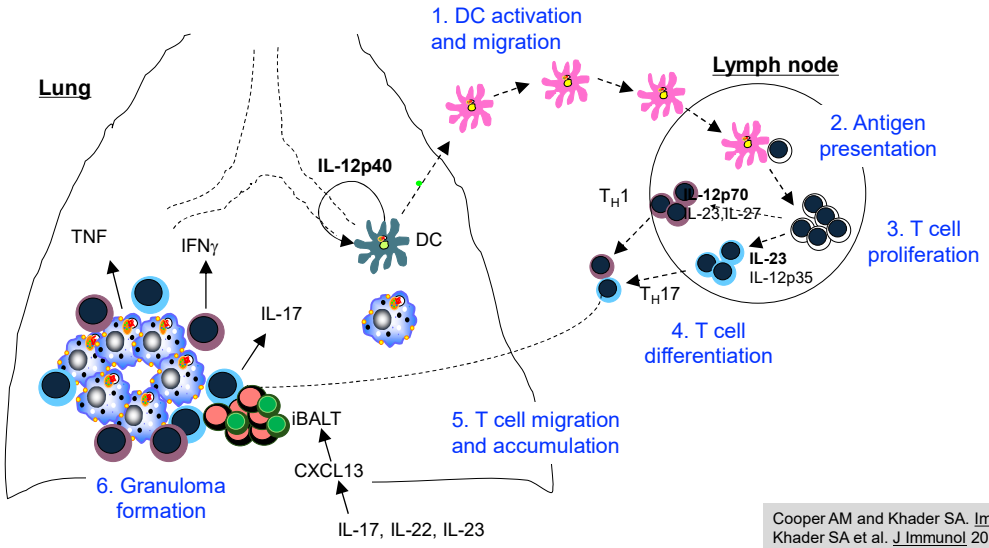
MTB

Immunological or disease phenotype	Symptoms?	TST	IGRA	CXR changes?	Bacterial burden
Highly effective innate immunity	No	Neg ("Resistors")	Neg	None	None
Highly effective adaptive immunity	No	Neg → Pos → Neg ("Reverters")	Pos → Neg	None to minimal (± calcified granulomas)	None
T cell priming → LTBI	No	Neg → Pos ("Converters")	(Neg) → Pos	None to minimal (± calcified granulomas)	+
Active TB disease	Yes	Pos (or Neg)	Pos (or Neg)	Yes	++++

Phagosome-lysosome fusion & autophagosome-lysosome fusion are key mechanisms by which macrophages kill *MTB*

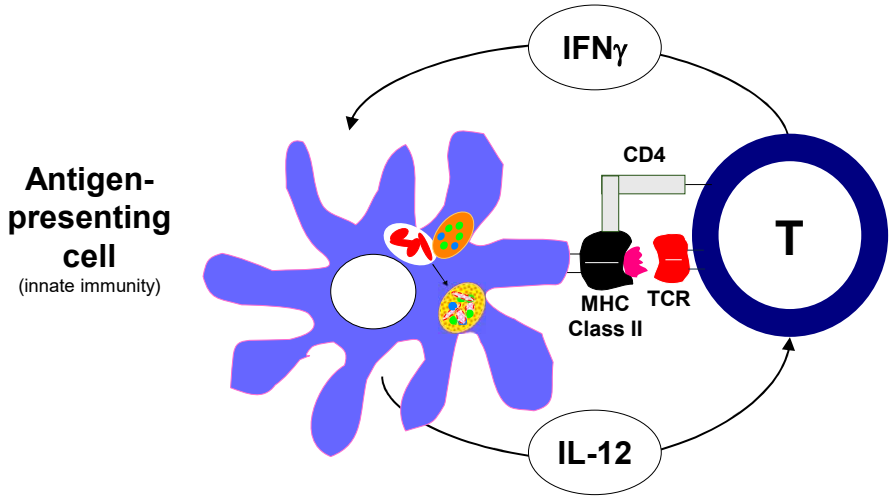


Overview of the initial innate and adaptive immune responses to *MTB* infection

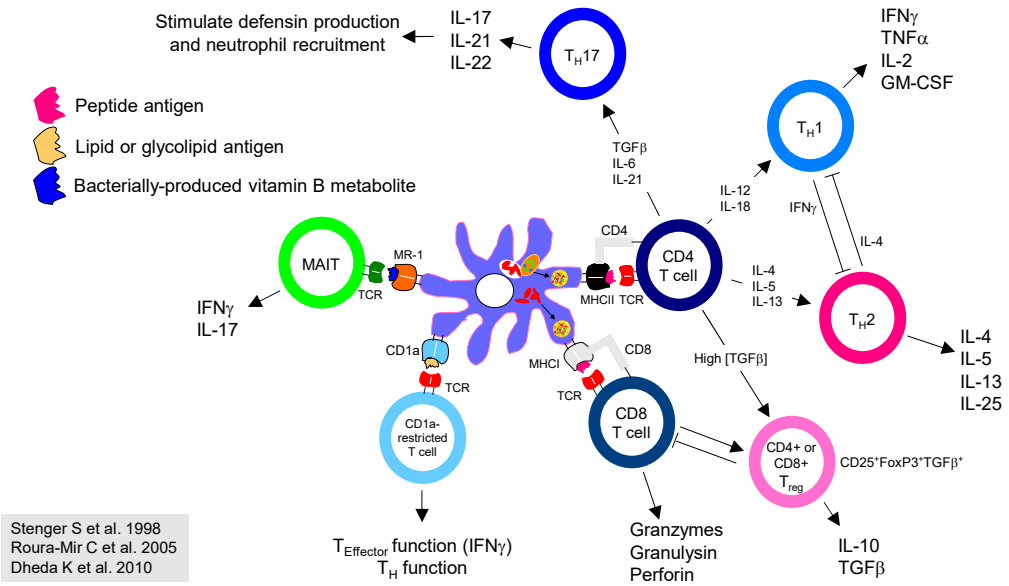


Cooper AM and Khader SA. Immunol Rev 2008
Khader SA et al. J Immunol 2011

A central component in the defense against *MTB*

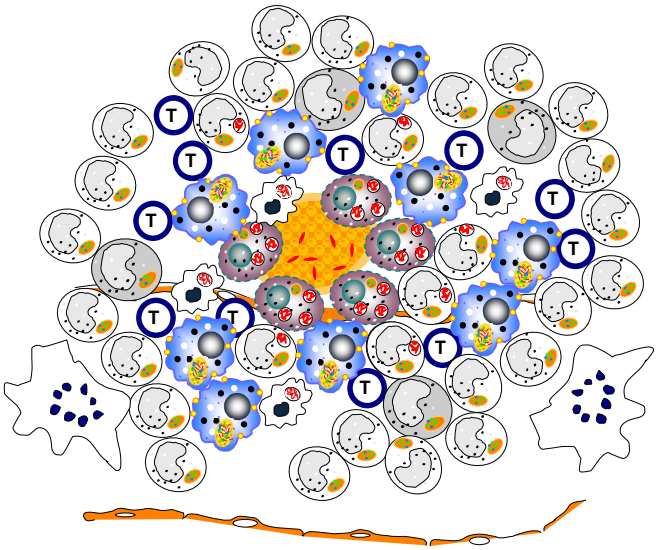


Innate-adaptive immune interactions are more complicated



Stenger S et al. 1998
Roura-Mir C et al. 2005
Dheda K et al. 2010

Granuloma: Chronic latent TB infection



Solid caseous center remains intact

↓

Any bug that escapes the caseous edge are ingested by highly activated macrophages

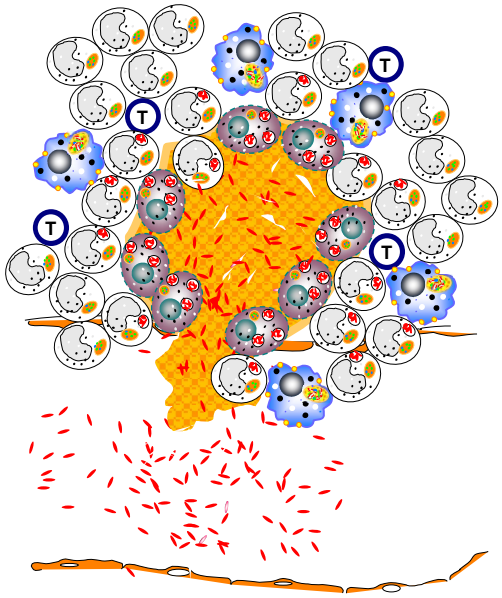
↓

Giant cells form
(a syncytium of epithelioid macrophages)

↓

If the caseation remains solid and does not liquify, **a chronic latent infection is established**

Granuloma: Decline in immunity



<u>Immunosuppression</u>
AIDS, cancer, anti-TNF, age, malnutrition

↓

Loss of integrity of granuloma

↓

Liquifaction of the caseous material ("caseous necrosis") provides a favorable medium for tremendous multiplication of *M. tb*.

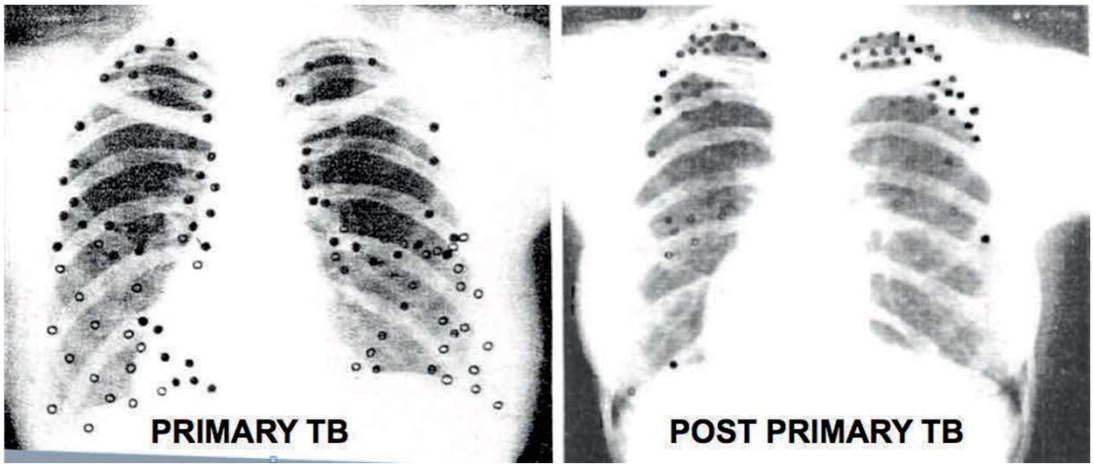
↓

Cavity formation

↓

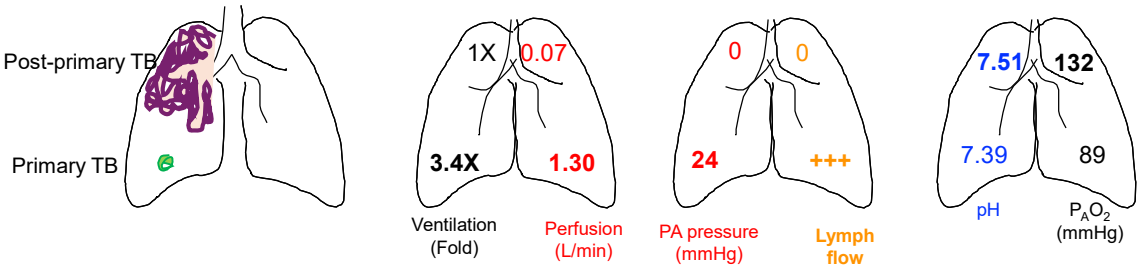
Rupture and spread to other parts of the lungs and to other individuals

Why is post-primary TB located mostly in the upper lung zones whereas primary TB (latent) mostly in the lower lung zones?



Medlar EM. *Am Rev Tuberc* 1948; 58: 583-611

Hypothesis: dormant *MTB* residing in the upper lobes are more likely to reactivate due to…



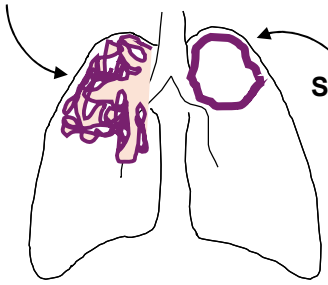
- Decreased blood perfusion → decreased influx of immune cells.
- Decreased lymph formation→ accumulation of mycobacteria & their antigens → increased DTH inflammation.
- Increased pH → increased aerobic glycolysis → attenuate autophagy.
- Increased alveolar O_2 due to decreased deoxygenated blood flow → increased growth of *MTB*.

Dock W. Arch Intern Med 1954
Dock W. Am Rev Tuberc 1946

West JB & Dollery CT. J Appl Physiol 1960
Murray JF. Am J Respir Crit Care Med 2003

Why do most cavities that form in post-primary TB occur in the upper lobes?

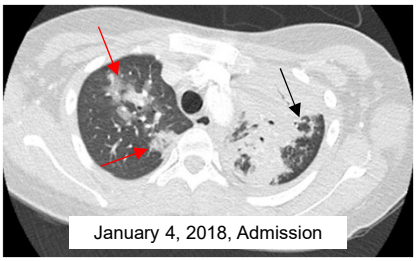
Decreased blood perfusion
Decreased lymph formation
Increased pH
Increased P_AO_2



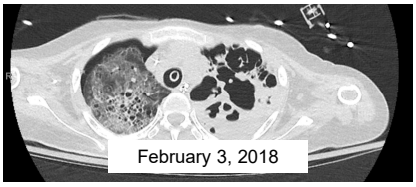
Stiffness 200 (kPa)
Stress 80 (kPa)

Stiffness 30 (kPa)
Stress 10 (kPa)

19-y.o. Marshallese woman post-partum



January 4, 2018, Admission



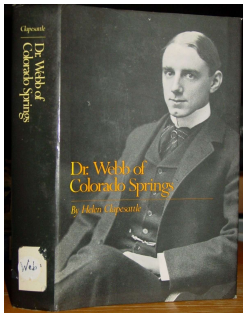
February 3, 2018

In the pre-antibiotic era, clinical observations showed that bedrest had therapeutic effects

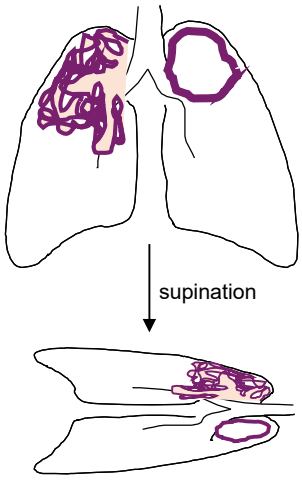
- I know I have hurt nobody by rest, but I am quite sure I often have by allowing them to exercise (Edward Livingston Trudeau, MD).
- A good rule is the following: Never stand when you can sit, never sit when you can lie down (Webb GB & Ryder CT. Overcoming TB: An Almanac of Recovery, 3rd edition).

National Jewish Hospital

New York



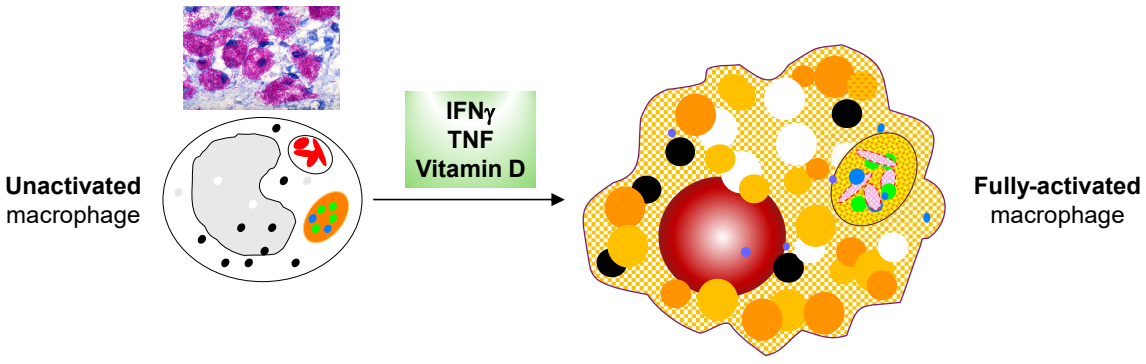
Is there rationale for bedrest in those with post-primary (upper lobe) TB?



Yes, it reverses all those physiologic variables that are deleterious to the host in the upright position!

- **Increased blood perfusion** → increased influx of immune cells.
- **Increased lymph formation and flow** → Increased efflux of *MTB* and antigens.
- **Decreased pH** → decreased aerobic glycolysis → increase autophagy.
- **Increased deoxygenated blood flow** → increased oxygen extraction by the blood → decreased P_AO2 → reduced growth of *MTB*.
- **Decreased expansion of chest** → decreased mechanical stress and alveolar size → decreased risk for cavitation or attenuation of cavity size.

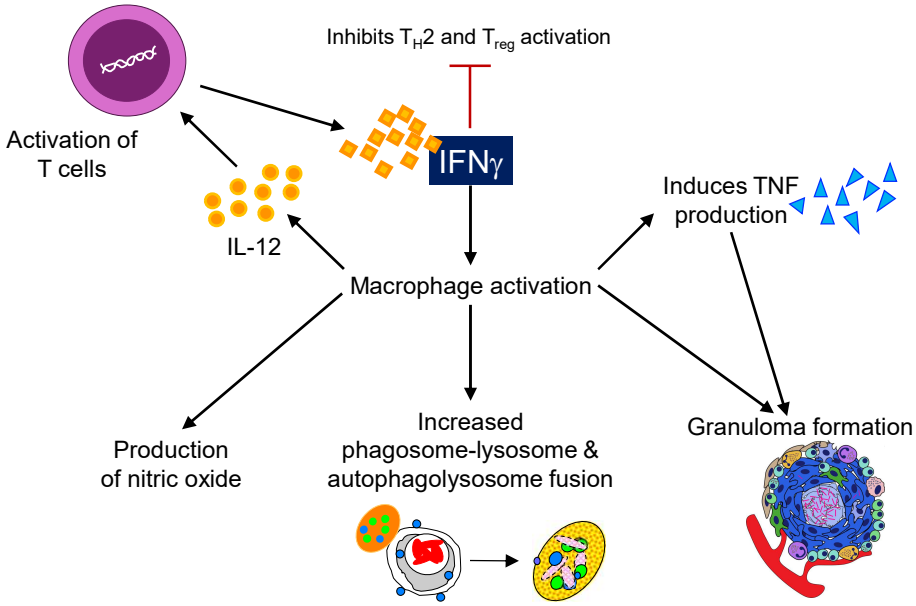
Three molecules that can activate macrophages



Summary of vitamin D & TB

- Circumstantial evidence (epidemiological / experimental) that vitamin D combats against TB.
- Studies are mixed on whether vitamin D supplementation helps resolve TB in humans.
- Just keep vitamin D at good (not toxic) level (30-50 ng/mL of 25-OH vitamin D).

How IFNγ is protective against TB



TNF and TB

- **Responsible for many clinical manifestations of TB:** fever, night sweats, weight loss, and tissue necrosis.
- **Responsible for host-defense functions against TB**
  - **TNF is critical for granuloma formation and TB control** by increasing the expression of adhesion molecules, NO, chemokines, and chemokine receptors.
  - **TNF helps mediate macrophage apoptosis**, an important feature of granulomas.
- **Mice with genetic disruption for TNF receptor** have increased morbidity and mortality from TB.
- ***Is there a more compelling evidence that TNF is important in controlling TB in man …?***

NEJM 2001; 345:1098

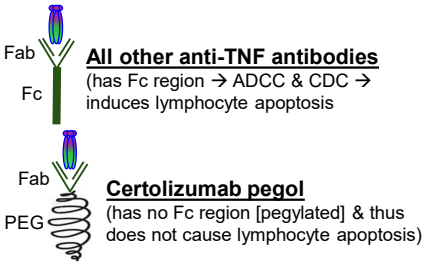
TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

- **Infliximab: a monoclonal antibody that neutralizes TNF**.
- **Method:** all reported cases of TB following infliximab therapy were examined: **70 patients**.
- **Strong circumstantial evidence** that inhibition of TNF increases the risk of reactivation TB:
  - TB was diagnosed a median of **3 months** *after* beginning infliximab.
  - In 48 patients, TB developed after **3 or fewer infusions**.
  - **56% had extra-pulmonary TB** (vs **~18%** for non-HIV individuals)
  - **24% had disseminated disease** (vs **< 2%** for non-HIV individuals).
  - Rate of **infliximab-associated TB** is ~4X **backgound rate** for RA.

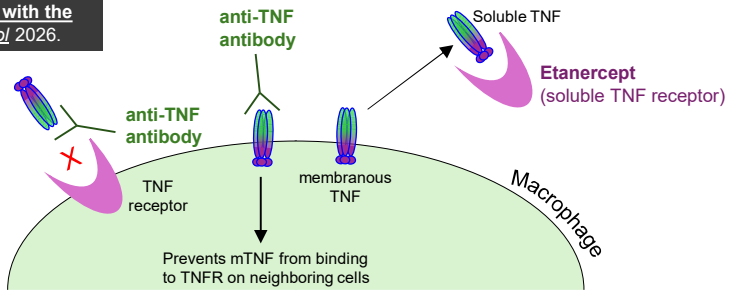
How do anti-TNF agents increase susceptibility to TB?

A systematic study of 19 studies (~400,000 patients taking TNF antagonist) → infliximab was associated with the highest risk for TB, followed by adalimumab and etanercept. Interestingly, **certolizumab pegol was associated with the lowest risk for active TB** (Lv X et al. *Front Immunol* 2026.



All other anti-TNF antibodies
(has Fc region → ADCC & CDC → induces lymphocyte apoptosis

Certolizumab pegol
(has no Fc region [pegylated] & thus does not cause lymphocyte apoptosis)



ADCC=antibody-dependent cell-mediated cytotoxicity

CDC=complement-dependent cytotoxicity

Anti-TNF inhibits *MTB*-induced IFNγ production (effect greater with anti-TNF antibody than etanercept)

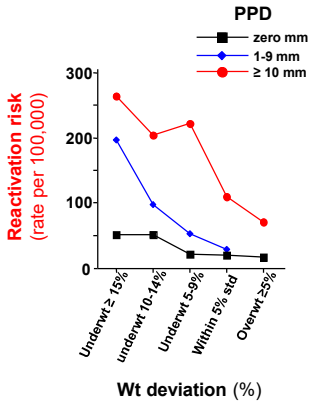
Anti-TNF inhibits apoptosis of macrophages (inhibiting a known killing mechanism of intracellular *MTB*)

Anti-TNF disrupts granuloma (as TNF is required for granuloma integrity)

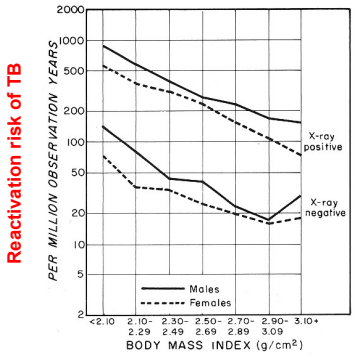
Anti-TNF reduces the number of $CD8^+CD45RA^+$ effector memory T cells (Bruns H et al. J Clin Invest 2009).

Is being thin a risk factor for TB?

68,754 U.S. Navy Recruits (1949-1951)
Palmer CE et al. *Am Rev Tuberc* 1957

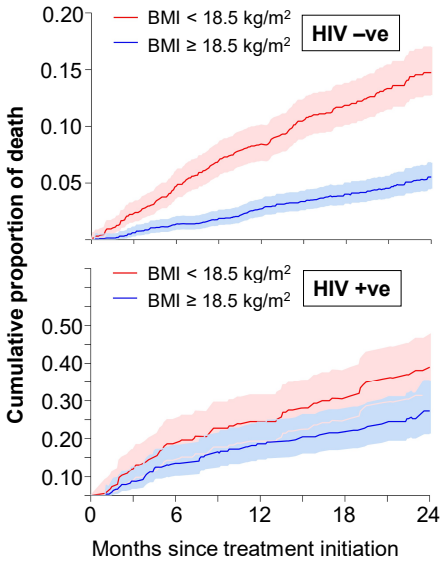


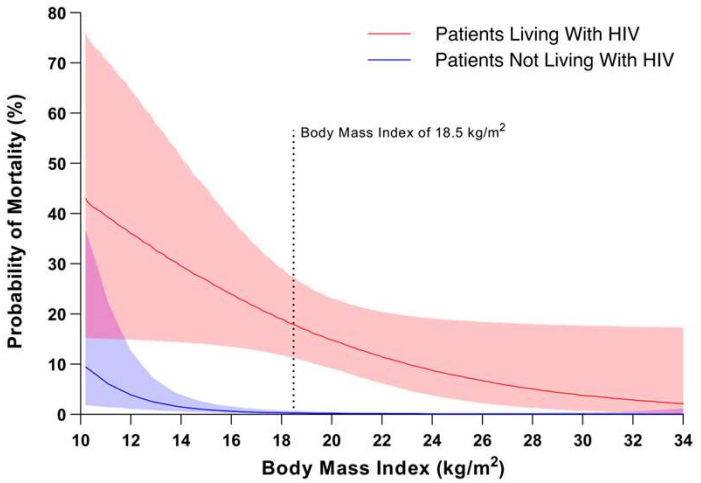
1,717,655 Norwegiens with compulsory miniature X-rays (1963-1975)
Tverdal A. *Eur J Respir Dis* 1986



Individual patient data-meta-analysis of RR/MDR-TB of low BMI (1993-2016: 5,148 patients from multiple countries)

Adjusted odds ratio of BMI<18.5 kg/m²:
- unfavorable outcome: 1.7
- death: 3.1





Campbell JR et al. Clin Infect Dis 2022

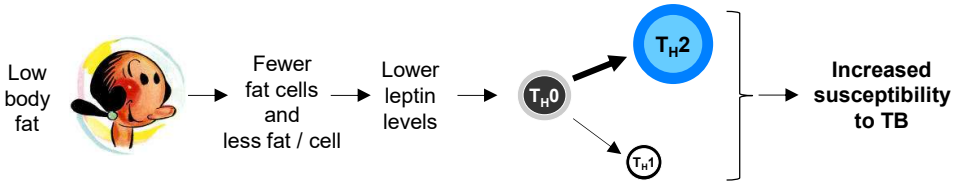
Q: Why are thin individuals more susceptible?

1. Hypothesis: due to a relative deficiency of leptin

2. Leptin is a satiety hormone produced by fat cells: the more fat one has → the more leptin is produced.

3. Leptin biases the immune response toward the T_H1 (IFNγ-producing) phenotype.

4. Thus, thin individuals → less leptin → less IFNγ-producing T_H1 cells.



5. Leptin-deficient mice are more susceptible to *MTB* and *M. abscessus*.

Wieland CW et al. Int Immunol 2005
Ordway D et al. J Leuk Biol 2008

Host risk factors for active TB

Acquired

- Originated from TB endemic country
- Extremes of age / post-partum status
- Thin body habitus / malnutrition
- AIDS & other acquired immunosuppression; e.g., cancer, organ transplant
- Immunosuppressives including GC and anti-TNF agent
- Tobacco smoke exposure
- Diabetes mellitus / ESRD
- Silicosis
- Vitamin D deficiency?

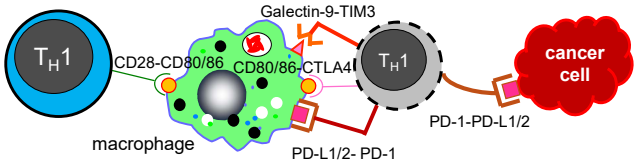
Hereditary

- Defects in the interferon-gamma-IL-12 axis
- Certain race or ethnicity? (controversial)
- Individuals with polymorphism of the vitamin D receptor, various cytokines, and polymorphism.

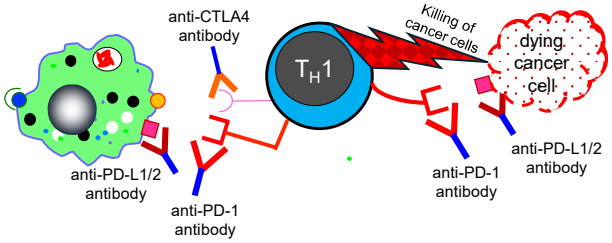
Poverty – underlying factor for malnutrition, crowded living conditions, and *MTB* exposure and infection.

Whether immune checkpoint inhibitors (ICIs) predispose to active TB is controversial

A) Immune checkpoints deactivate T_H1 cells



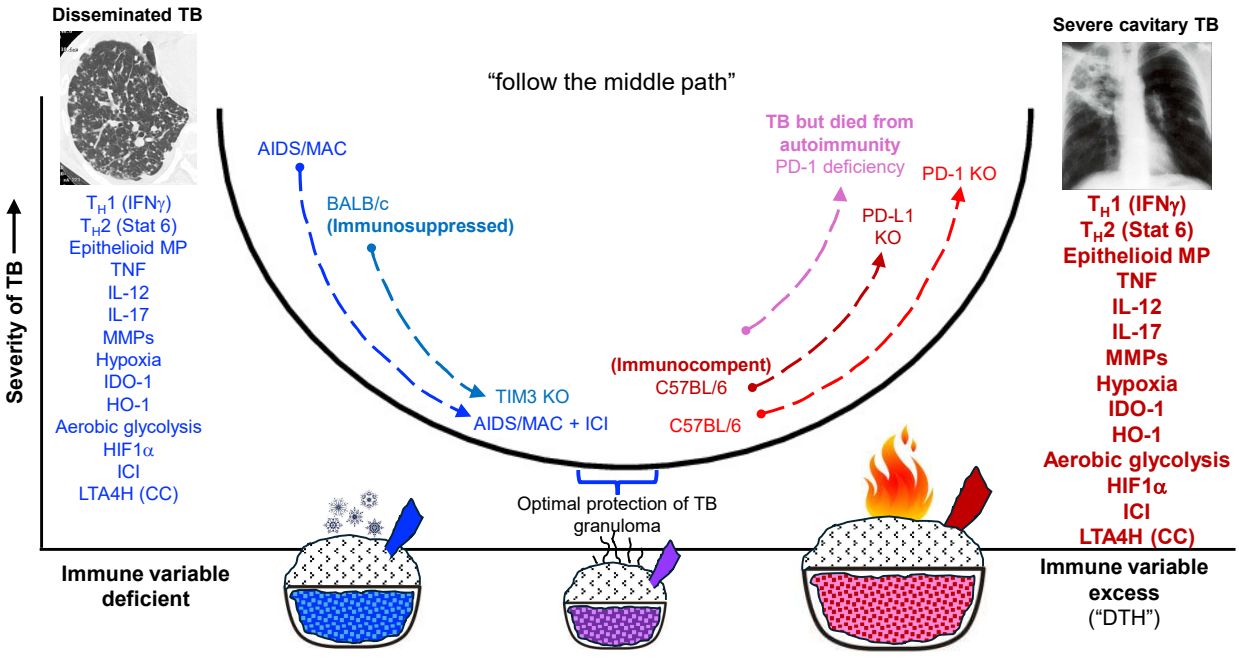
B) **Immune checkpoint inhibitors** activate T_H1 cells to kill cancer cells



Q: Since ICIs (*e.g.*, anti-PD1 antibody) augment IFNγ⁺T_H1 cell activity, would you predict mice *knocked out* for PD-1 (which would increase IFNγ⁺T_H1 cell activity) be more protective against *MTB*?

A: Yes, I would also predict that mice *knocked out* for PD-1 (which would increase IFNγ⁺T_H1 cell activity) be more protective.

But in reality, PD-1 KO mice were actually **more susceptible** to TB, with increased *MTB* burden and reduced survival.



Three test questions

Which statement is true about leptin?

A. It skews T cells toward the T_H1 (IFNγ-producing) phenotype.
B. It causes increase appetite and weight gain.
C. Its levels are high in thin individuals.

Which statement is false regarding vit D and TB?

A. Deficiency of sunlight can result in vit D deficiency and theoretically increase the risk for TB.
B. Since it is a water soluble vitamin, it is safe to take vit D in "large" doses.
C. Vit D can induce the production of a protein that can directly kill intracellular *MTB*.
D. Vit D enters the cell nucleus and directly turns on certain genes.

Which statement is true about AIDS and TB?

A. TB in patients with advanced HIV+ve is associated with well-formed granulomas.
B. It illustrates the importance of $CD4^+$ T-cells in the defense against TB.
C. It is associated with increased levels of IFNγ.