Host Risk Factors for NTM Infections

(and a little bit on immunopathogenesis)

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To combat mycobacteria, *"follow the middle path."*

Buddha

NTM Lecture Series
April 25, 2024, 10:15-11:00 AM

No conflict of interests

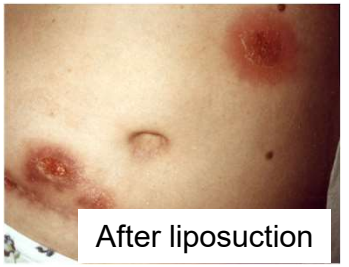
Outline & goals

- **Underlying host risk factor dictates type of NTM disease**
  - Disseminated / extrapulmonary visceral NTM disease
  - Skin, soft tissue, and traumatic orthopedic infections
  - Isolated NTM lung disease
  - NTM lung disease without obvious risk factors

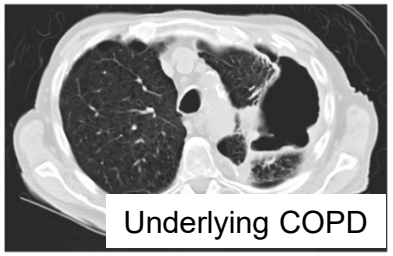
- **Immunopathogenesis based on the Goldilock's concept**
  - Using *immune checkpoint inhibitors* as an example
  - Expanding on the concept to other entities

The type of NTM disease reflects the underlying host risk factor

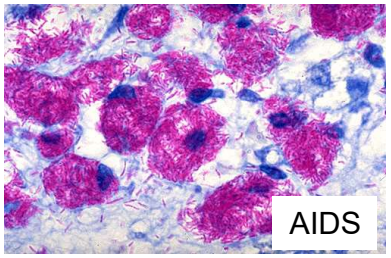
Skin, soft tissue, and/or traumatic orthopedic NTM infection
(most have normal immunity)



Isolated NTM lung disease
(structural lung abnormality)



Extrapulmonary visceral or disseminated NTM infection (essentially all have underlying severe immunodeficiency)



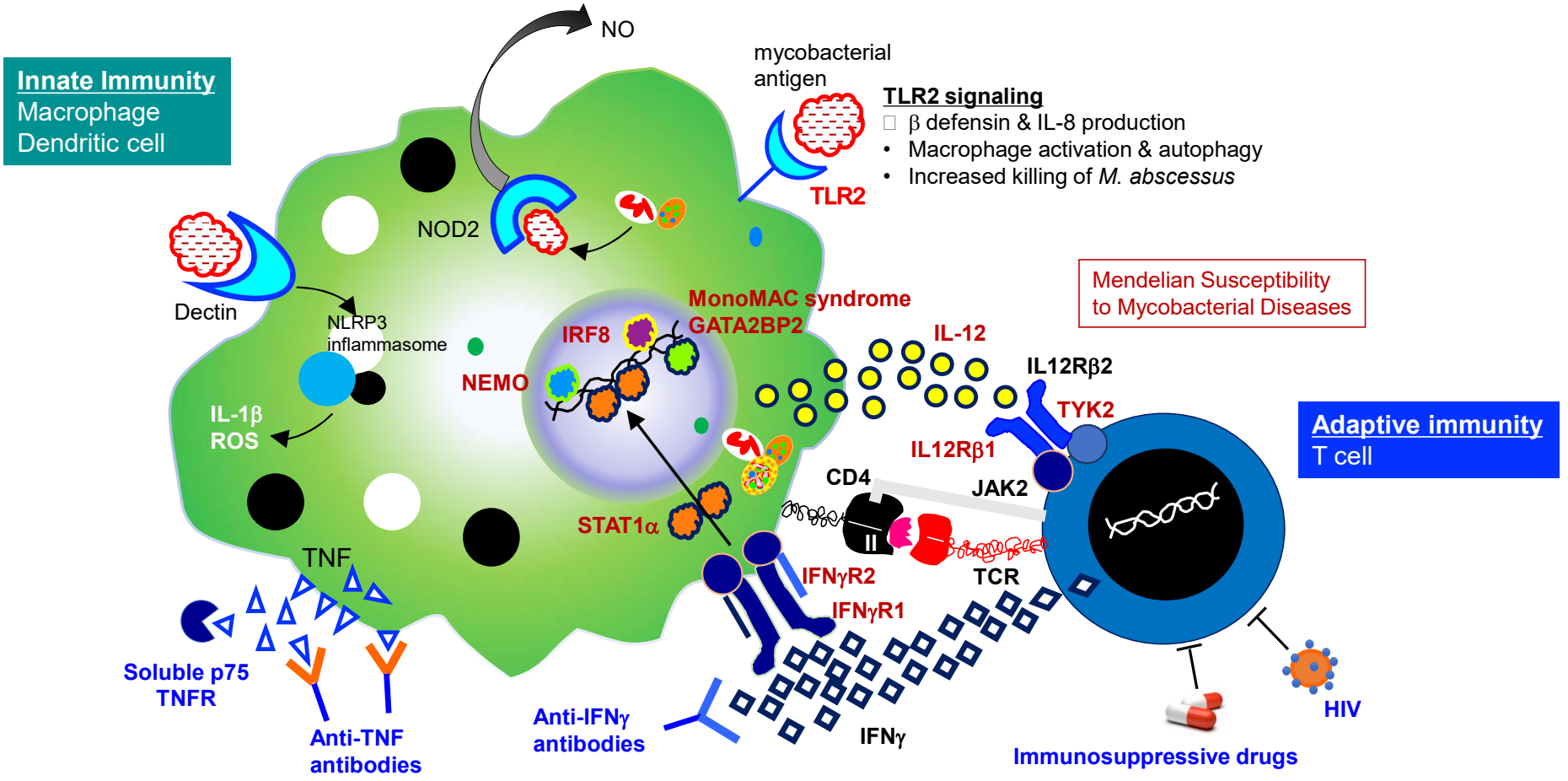
What medical condition am I alluding to with this blood collection tube?

Dupont isolator

AIDS

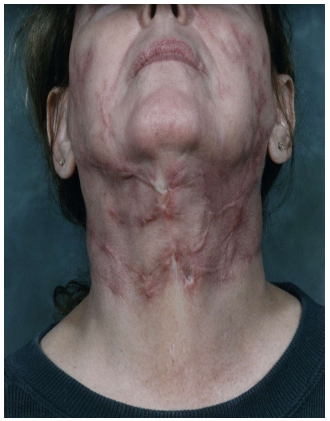
Patients with advanced AIDS are susceptible to disseminated (MAC) because they have depletion of $CD4^+$ cells that produce IFNγ

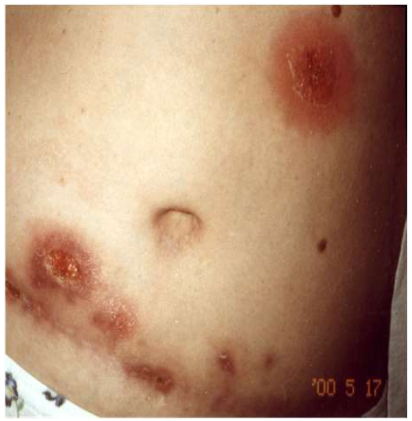
Acquired and inherited disorders that predisposes to disseminated mycobacterial infection



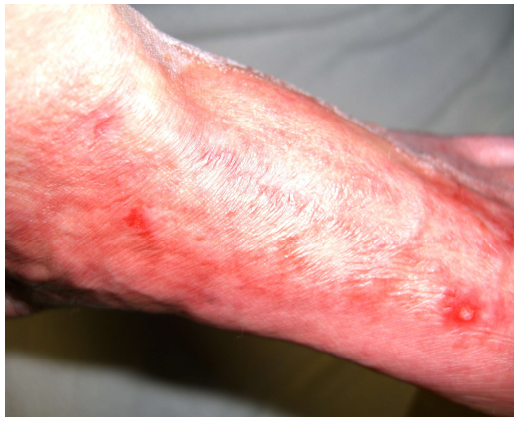
Risk factors for skin, soft tissue, and traumatic orthopedic NTM infections

- **Breach of skin** – accidental trauma, foot salons, medical procedures with contaminated water, instrument, or medications.


After cosmetic surgery



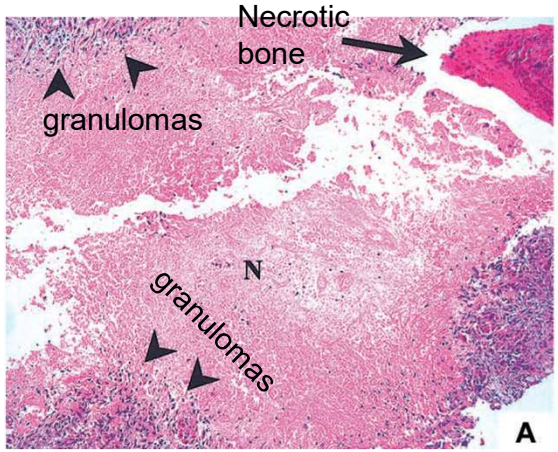
After liposuction


After bunionectomy

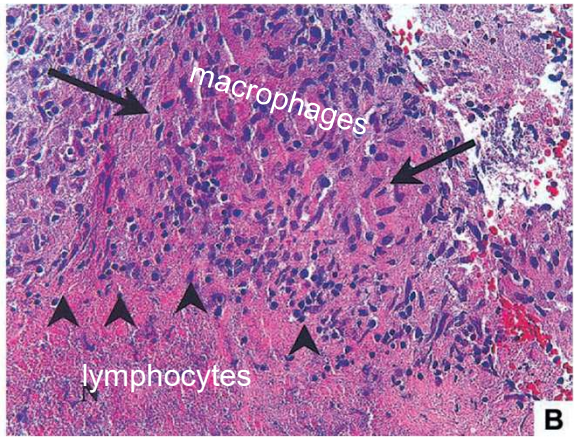
- Most cases occur in those with normal host immunity…but we contend that physical trauma itself may be immunocompromising.

Why did this healthy teenager get a localized NTM infection of the spine?

- A 16-year-old girl suffered multiple falls from competitive roller skating, resulting in abrasions, MSK pains, and recalcitrant backache.
- MRI revealed an enhancing signal in T9 with anterior paraspinal soft tissue mass from T8-T10.
- Biopsy of T9 revealed necrotizing granulomas and culture was +ve for *M. abscessus.*



T9 vertebra biopsy

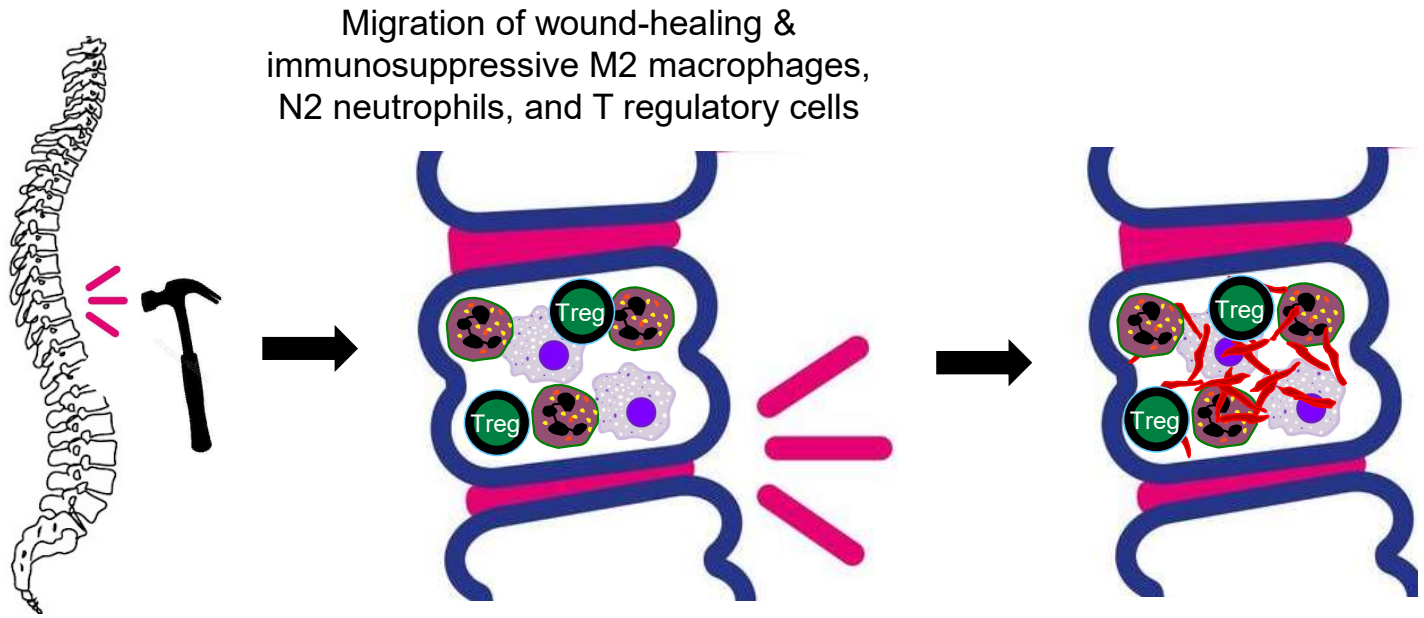


Higher power of granuloma

Mike Iseman, MD

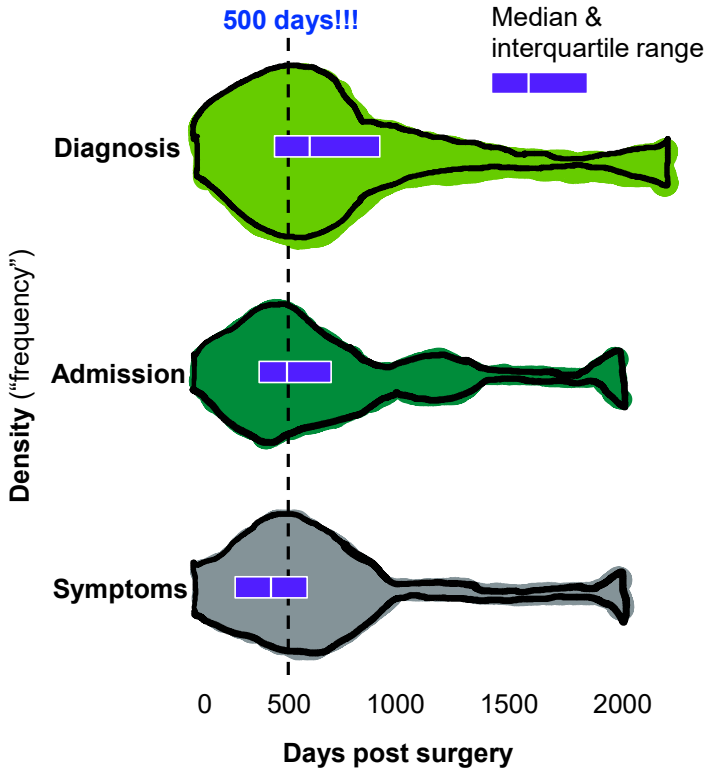
~~We~~ hypothesized that the site of trauma is "fertile soil" for seeding of infection

"locus minoris resistentiae"



M. chimaera and open-chest heart surgery

- In 2013, *M. chimaera* infections were reported in patients who underwent open-chest heart surgery.
- Infections involved the **implanted hardware**, **surgical wounds**, and/or **internal organs**.
- *M. chimaera* was traced to **contaminated heater-cooler units** (“heart-lung machine”) and the bioaerosols generated, which contaminated the surgical sites.

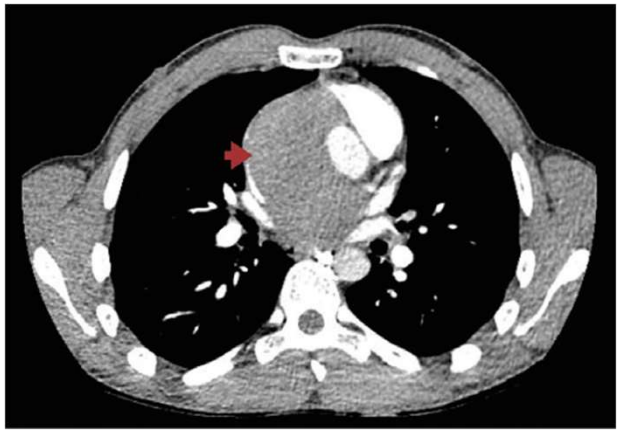


Scriven JE et al. Clin Microbiol Infect 2018

M. chimaera and open-chest heart surgery

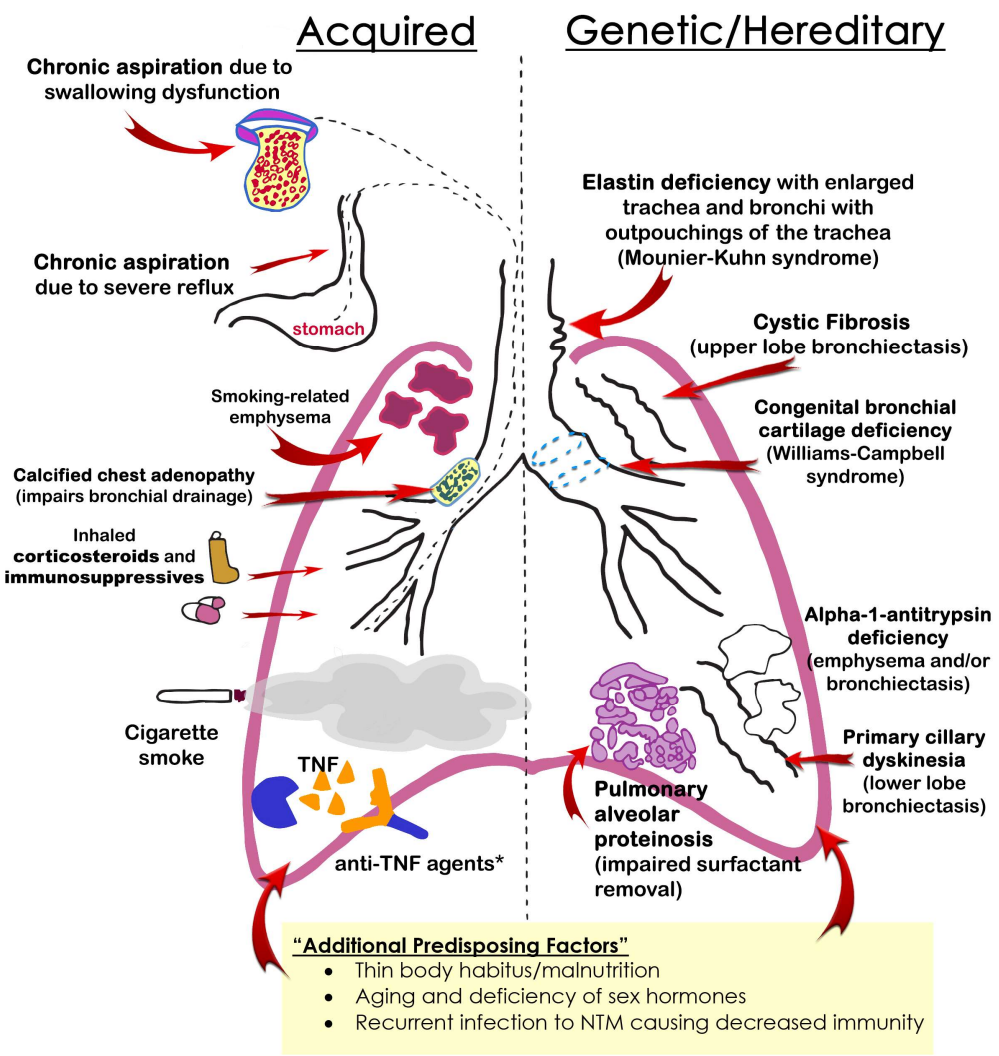
AORTIC & AORTIC VALVE SURGERY are HIGHEST RISK ⟷ Coronary artery bypass graft surgery is lowest risk

- A 22-year-old man had undergone mechanical aortic valve replacement.
- He presented **~1.5 years later** with drenching night sweats & chest pains.
- Aortic dissection with pseudoaneurysm with false lumen (red arrow).
- Underwent prosthetic aortic grafting with intraoperative tissues +ve for *M. chimaera*.

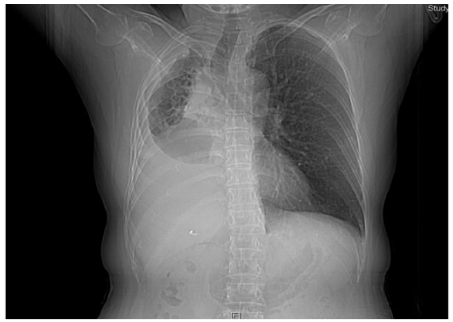


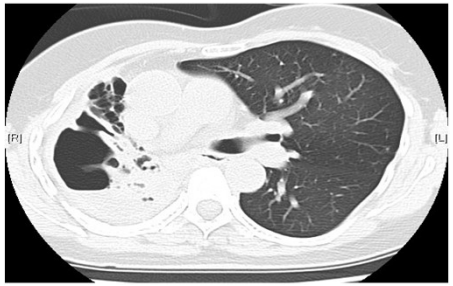
O'Neil CR et al. OFID 2018

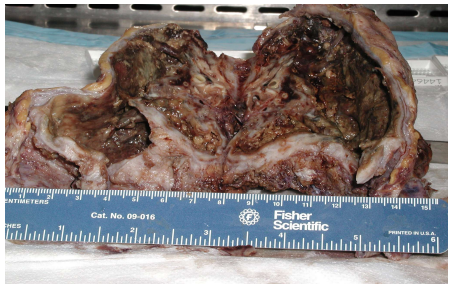
Risk factors for NTM lung disease



55-year-old Asian woman from Hawaii with remote history of TB

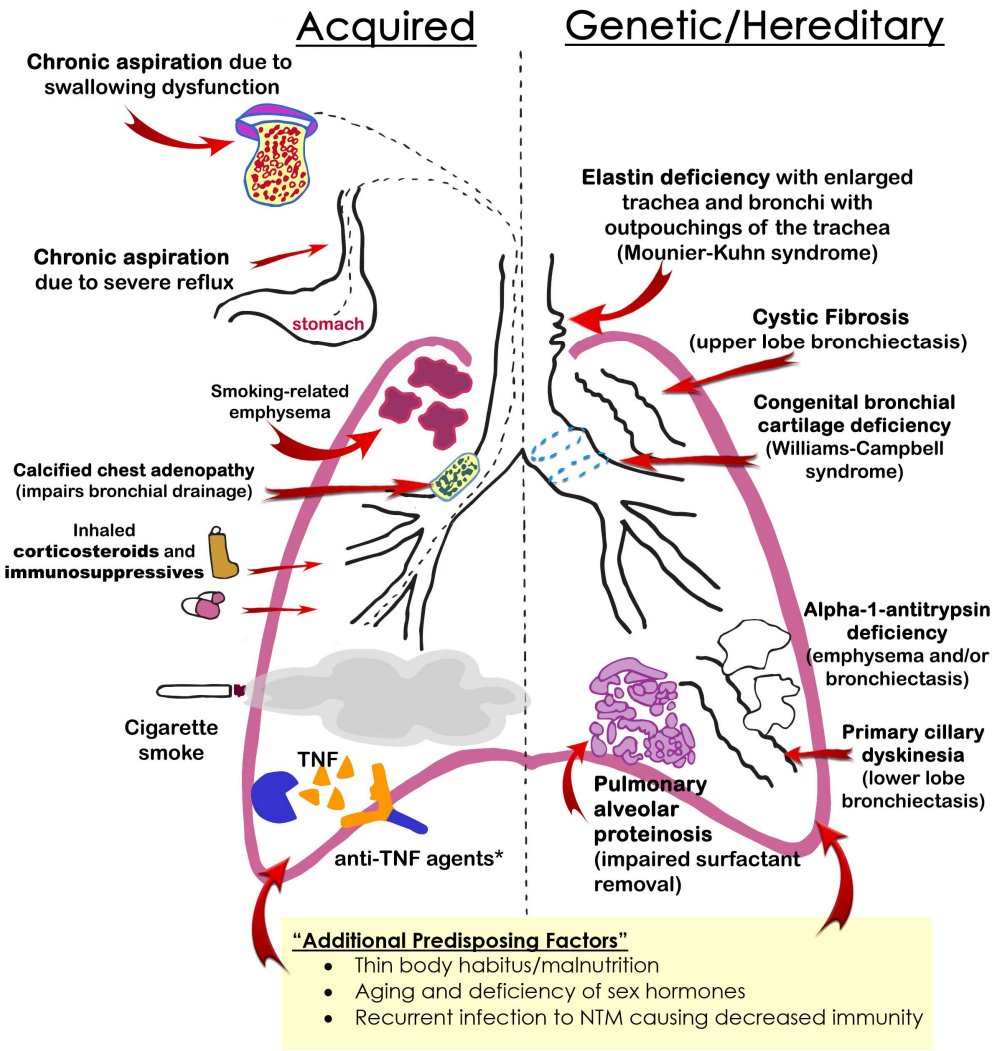


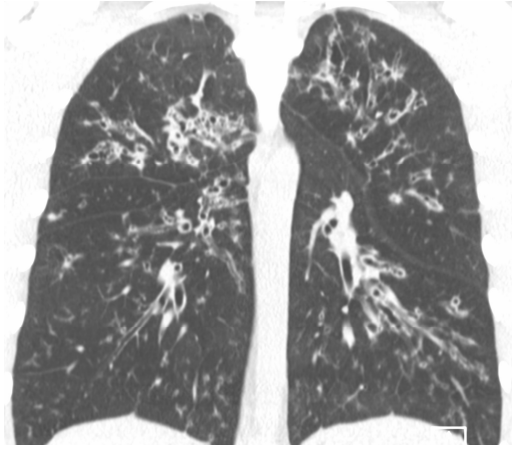




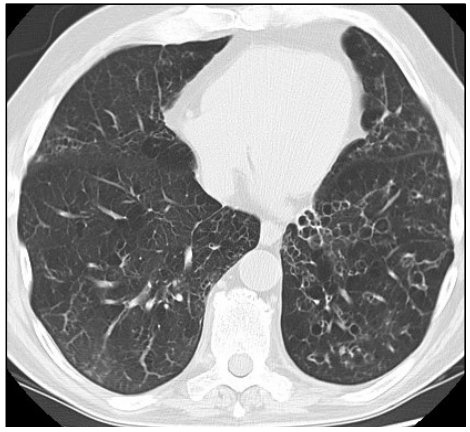
John D. Mitchell, MD
Extrapleural pneumonectomy
Oct 2006

Q1: What are the underlying causes for BXSIS ± NTM-LD ?



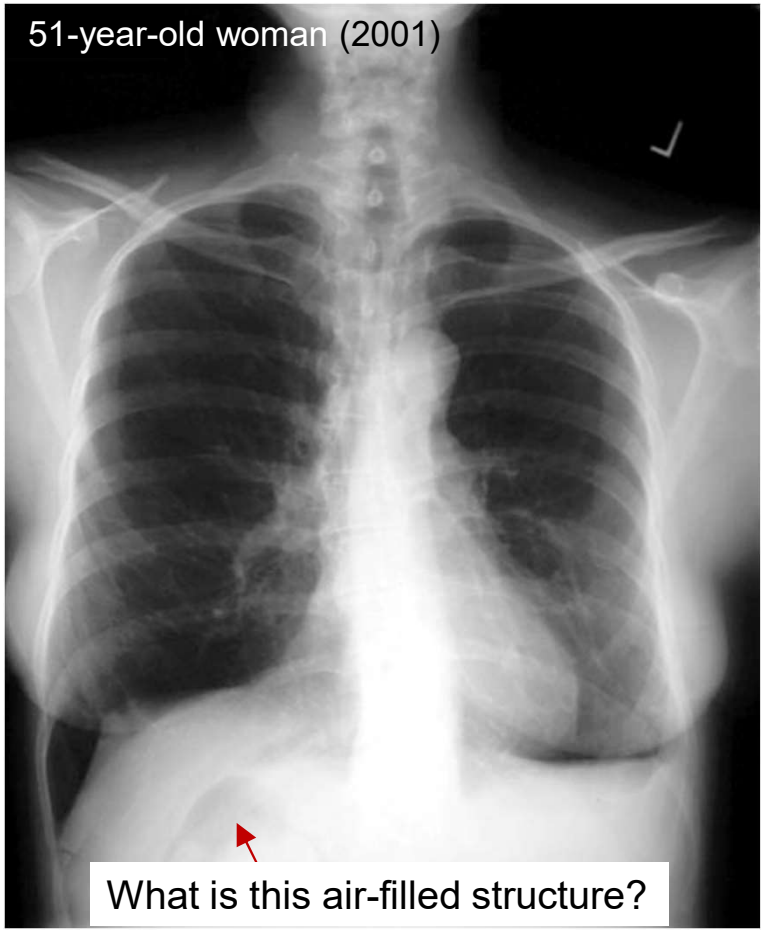


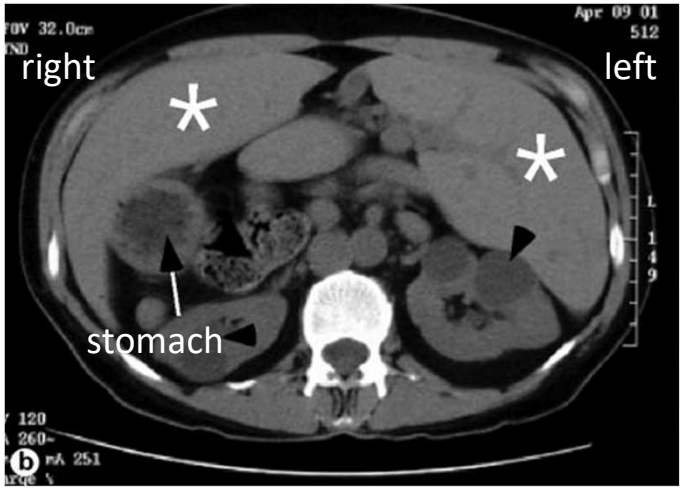
A 66 –year-old woman with CF

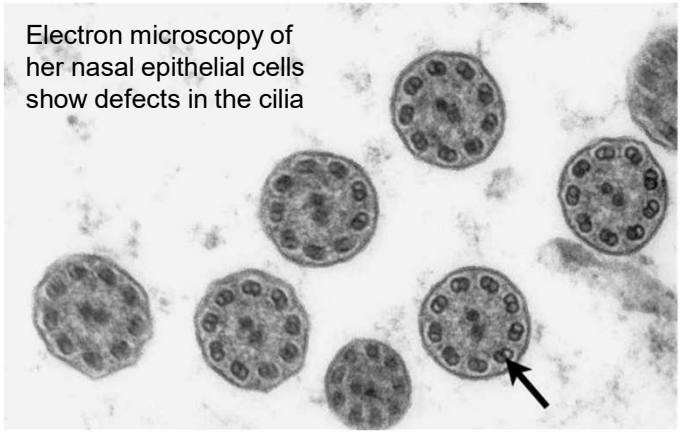


A 65 –year-old man with alpha-1-antitrypsin deficiency

Q2: What is the underlying cause for the BXSIS + NTM-LD?

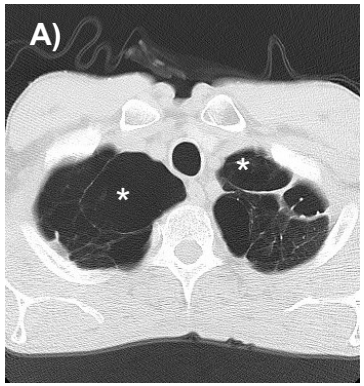


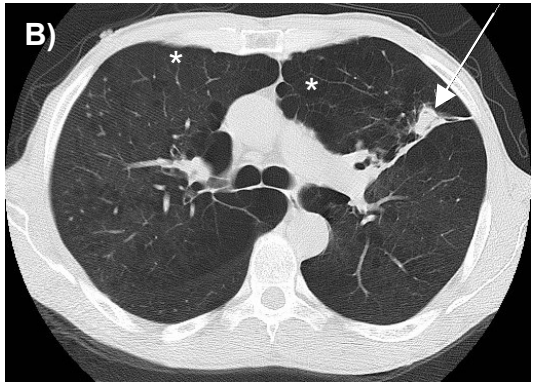


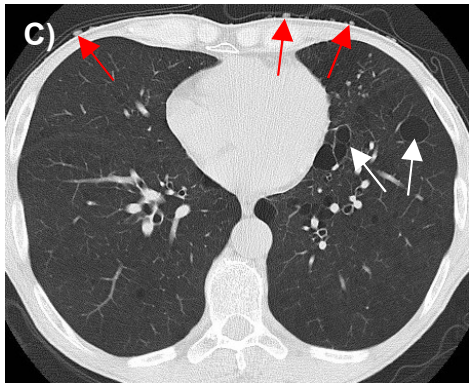


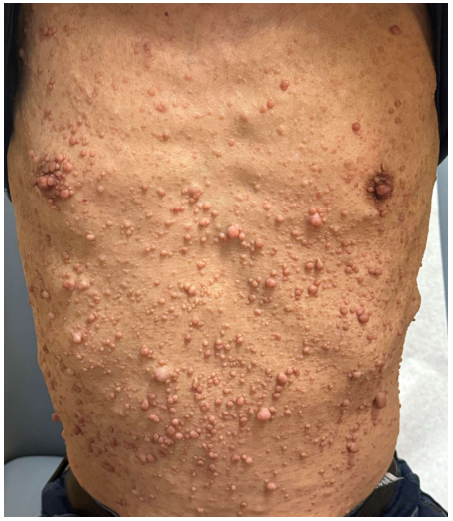
She has **primary ciliary dyskinesia** resulting in situs ambiguous of her internal organs

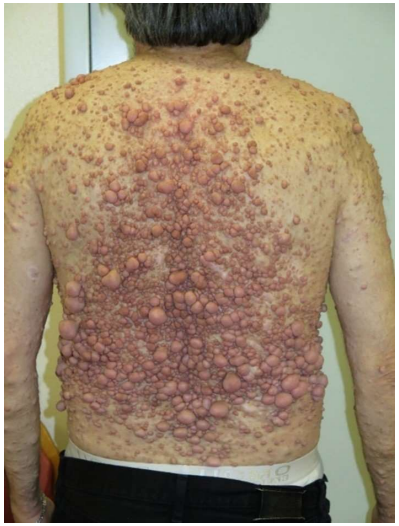
Q3: What is the underlying cause for the emphysema, lung cysts, and *M. avium* complex-LD in a 63-year-old male veteran?



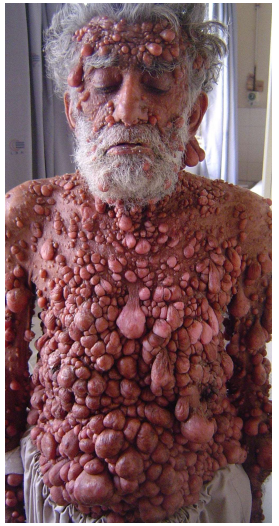








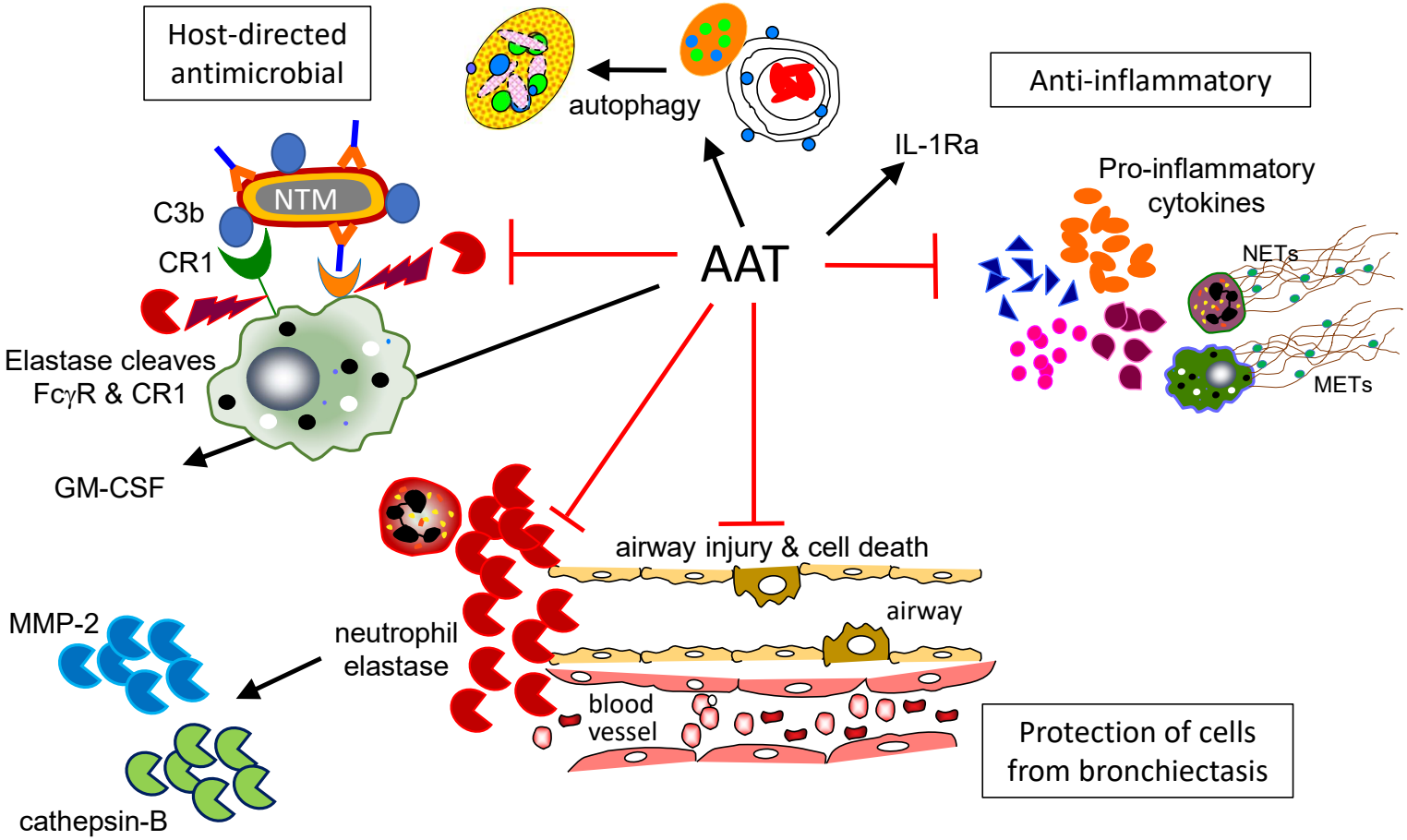
Not the same patient



Not the same patient

Neurofibromatosis
(von Recklinghausen's disease)

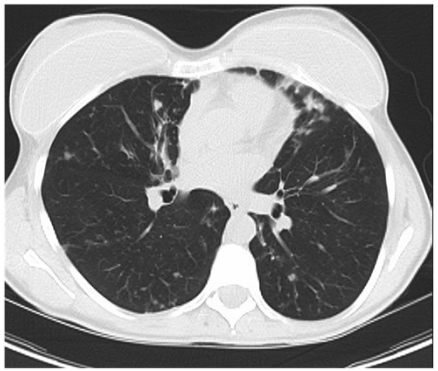
AAT has a panoply of effects that protects against NTM lung disease

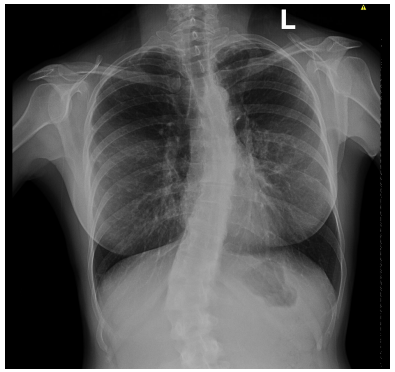


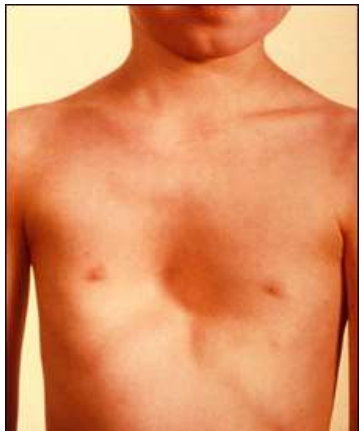
What about those without obvious risk factors?

- A significant number have a life-long slender body habitus, scoliosis, & pectus excavatum.

A 41-year-old previously healthy woman life-long slender body habitus, severe scoliosis, and NTM lung disease



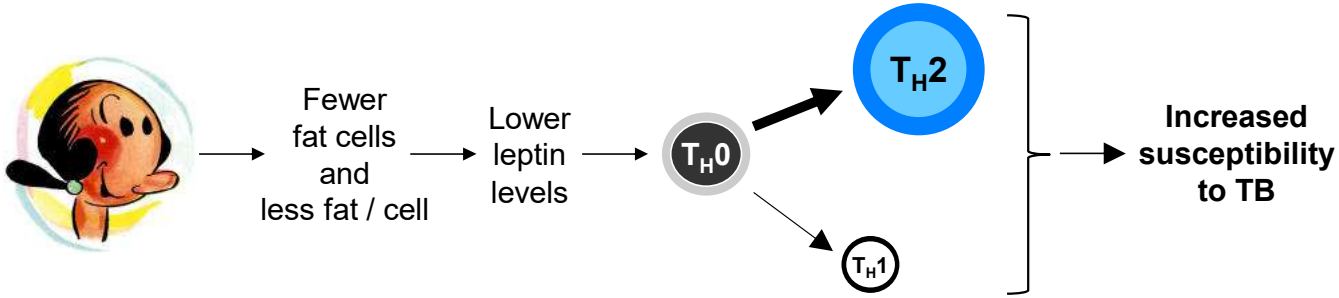




- Reich and Johnson described 29 patients (all women with no obvious risk factors) with NTM lung disease, localized mostly in the right middle lobe and lingula (Chest 1992).
  - They coined the eponym “Lady Windermere syndrome” because they posited that some women are more vulnerable to NTM-LD because of “voluntary cough suppression.”
  - While they did not allude that these patients have slender body habitus or thoracic cage abnormalities, “Lady Windermere syndrome” has become synonymous with women with NTM-LD with this body phenotype.

If thin individuals are more susceptible (as has well documented with TB), why could that be?

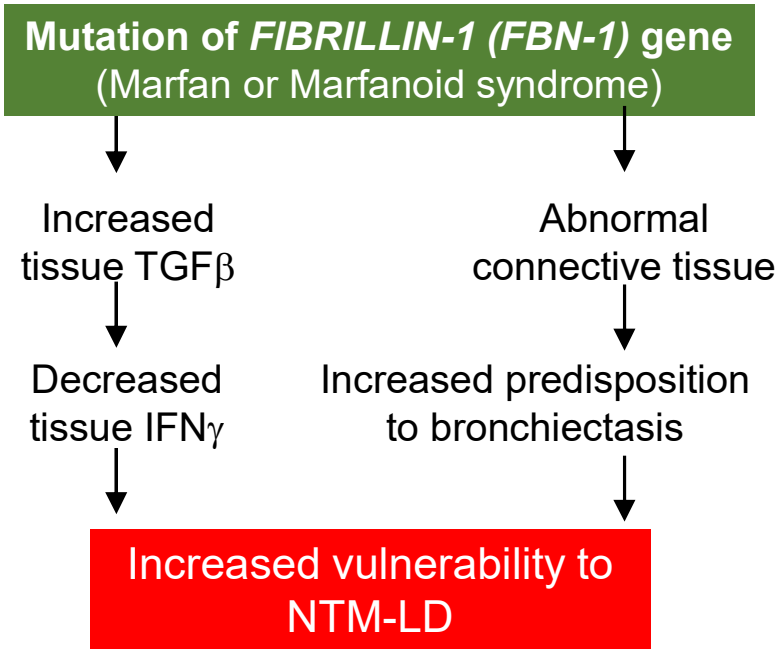
- Hypothesis: due to a relative deficiency of leptin.
- Leptin is a satiety hormone produced by fat cells: the more fat one has → the more leptin is produced.
- Leptin also skews the adaptive immunity toward the host-protective T_H1 (IFNγ-producing) phenotype.
- Thus, thin individuals → less leptin → less IFNγ-producing T_H1 cells.

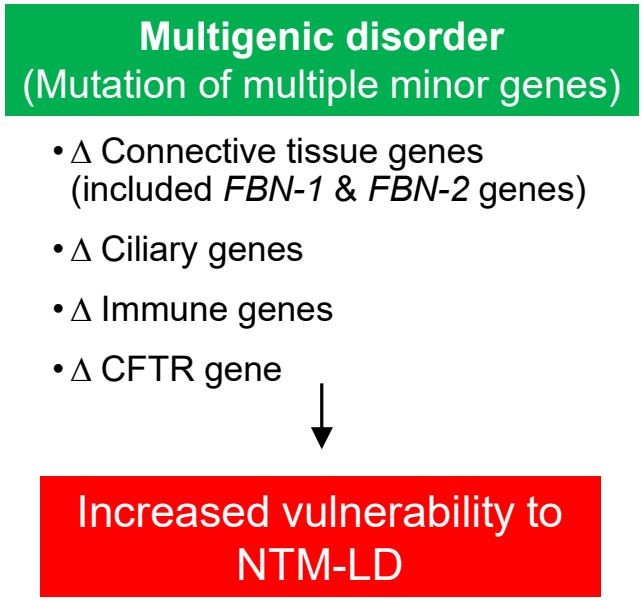


- Leptin-deficient mice are more susceptible to *M. tuberculosis* and *M. abscessus*.

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

Other hypotheses of why patients without obvious risk factors get NTM-LD





Kartalija M et al. Am J Respir Crit Care Med 2013
Daniels ML et al. Ann Am Thorac Soc 2016
Tun MH et al. J Thorac Dis 2021
Szymanski EP et al. Am J Respir Crit Care Med 2015

Whole Exome Gene Sequencing of 11 NTM-LD patients with PEX/scoliosis

Patient number	Study No.	%body fat or BMI	PEX	Scoliosis	Key gene variant found
1	63682	21%	Yes	Yes	Δ*fibrillin-1*, Δ*IFNγR1*
2	63690	21%	Yes	Yes	***ΔMST1R***
3 (sister of 2)	63685	17.5 kg/m^2	Yes	Straight back	***ΔMST1R***
4	63688	25%	Yes	Yes	
5	63683	21.5 kg/m^2	Yes	Yes	Δ*TGFβ-induced protein*
6	63687	28%	Yes	Yes	
7	63684	25%	Yes	Yes	
8	63686	27%	Yes	Yes	
9	63692	25%	Yes	Yes	***ΔMST1R***
10	63691	21 kg/m^2	Yes	Yes	***ΔMST1R***
11	63689	23 kg/m^2	Yes	Yes	

Targeted Sanger sequencing of 29 pNTM patients without PEX or scoliosis do NOT have ΔMST1R

MST1R = cell surface receptor with tyrosine kinase activity involved with ciliary function

Take home points

Skin, soft tissue, and/or traumatic orthopedic NTM infection

Most have normal underlying immunity but trauma itself is immunosuppressive

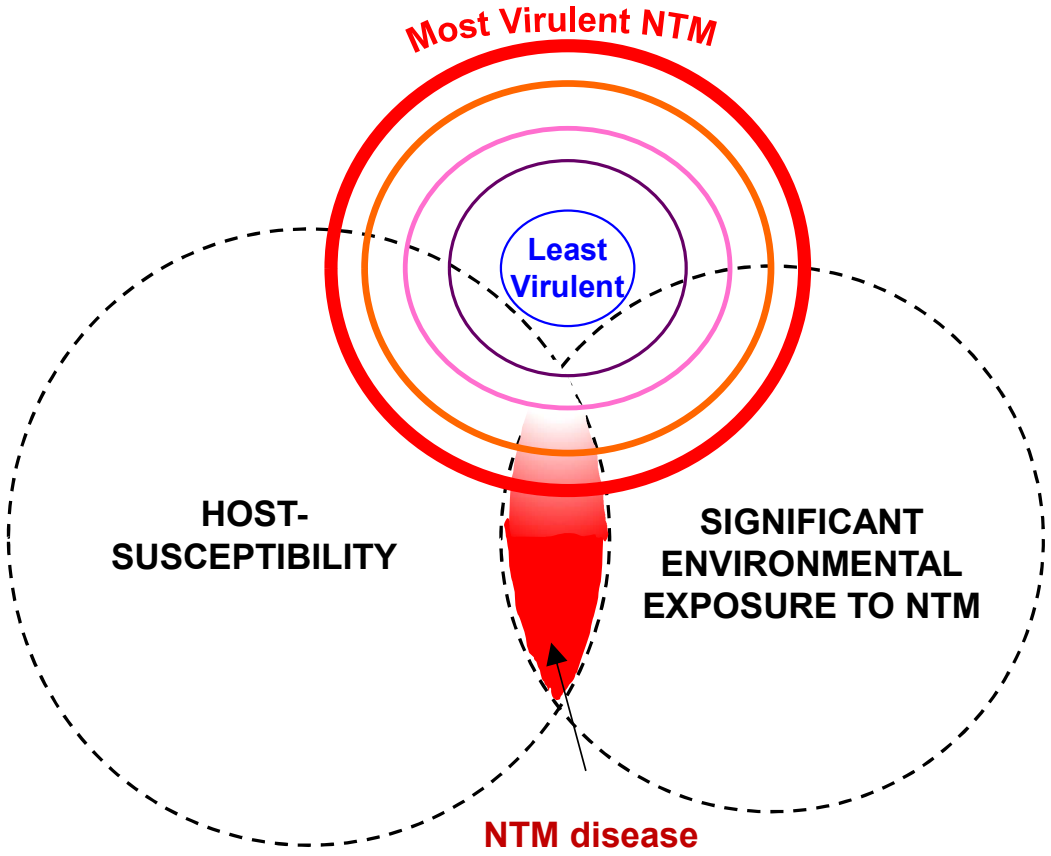
Isolated NTM lung disease

Most have underlying structural lung abnormality (BXSIS or emphysema): e.g., CF, AAT deficiency, multigenic

Extrapulmonary visceral or disseminated NTM infection

Essentially all have underlying severe immunodeficiency & one should search for it

The intersection of: 1) host susceptibility, **2)** exposure, & **3)** NTM virulence dictates whether NTM disease develops



Q4: Which of the following patients is likely to have a functional defect in IFNγ signaling / function?

a. A 60-year-old man with COPD and cavitary *M. avium* lung disease.

b. A 60-year-old woman with isolated *M. avium* lung disease of the lingula, RML, and RUL.

c. A 4-year-old girl with disseminated *M. avium*.

d. A 25-year-old man with surgical wound foot infection after bunionectomy.

Q5: Which of the following are risk factors for isolated NTM lung disease? *More than one may be correct.*

a. Pulmonary alveolar proteinosis

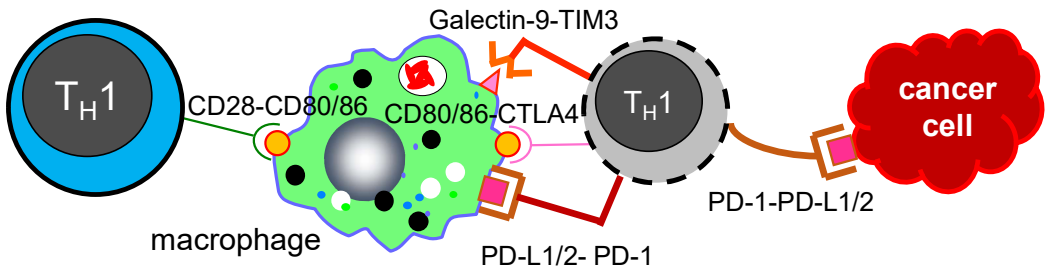
b. Emphysema

c. Auto-antibodies to IFNγ

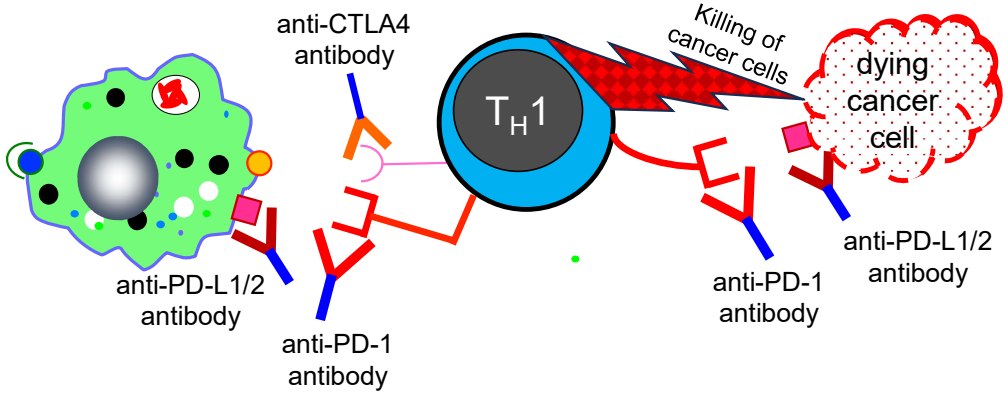
d. Idiopathic bronchiectasis

Immune checkpoint inhibitors (ICIs) have revolutionized treatment of many cancers

A) Immune checkpoints deactivate T_H1 cells



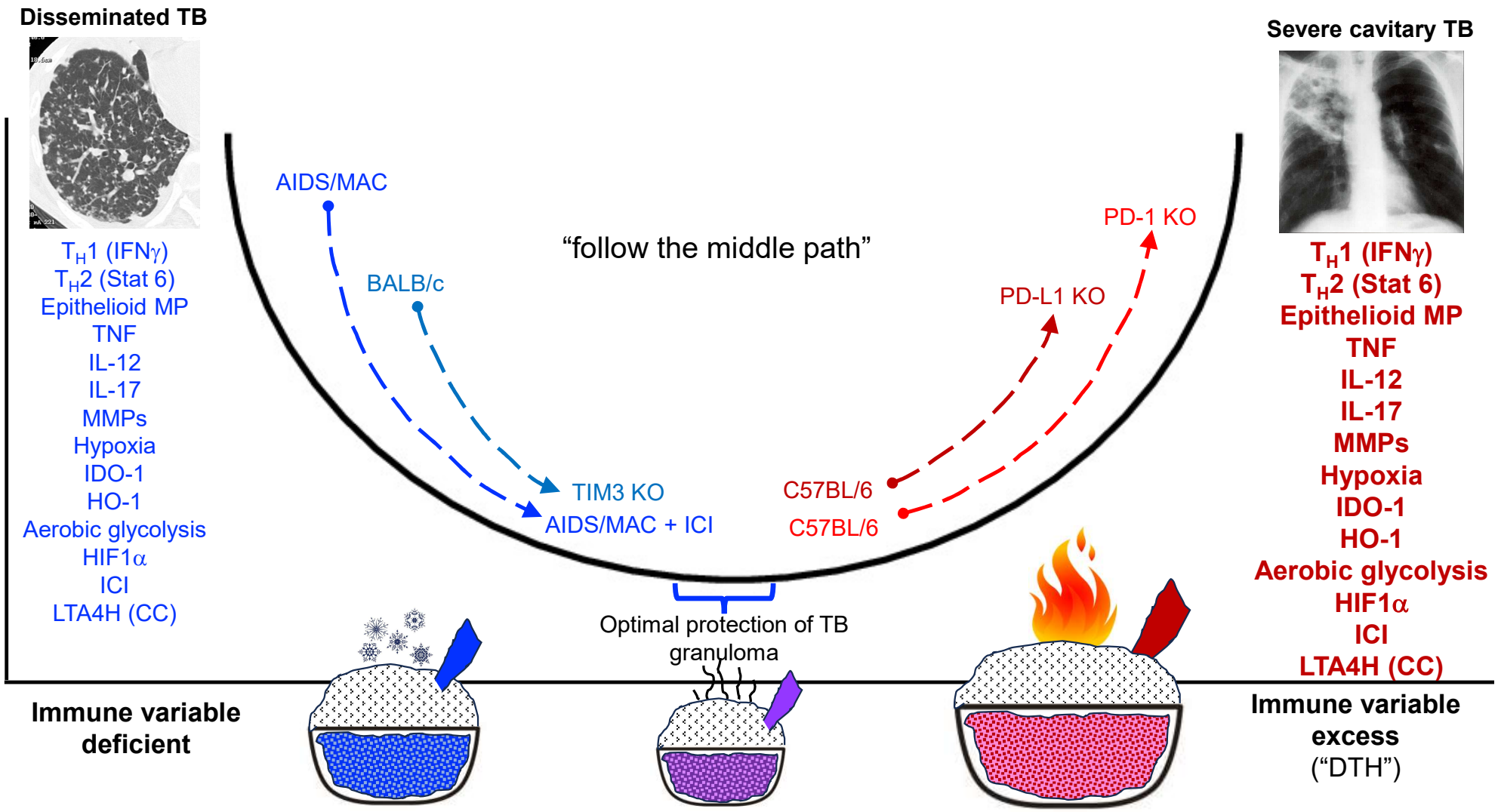
B) **Immune checkpoint inhibitors** activate T_H1 cells to kill cancer cells



Q6: Since ICIs (*e.g.*, anti-PD1 antibody) augment IFN$\gamma^+$$T_H1$ cell activity, would you predict mice *knocked out* for PD-1 (which would increase IFN$\gamma^+$$T_H1$ cell activity) be more protective against *MTB*?

A6: Yes, I would also predict that mice *knocked out* for PD-1 (which would increase IFN$\gamma^+$$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.


Disseminated TB
Severe cavitary TB
Severity of TB
AIDS/MAC
BALB/c
"follow the middle path"
PD-1 KO
PD-L1 KO
TIM3 KO
AIDS/MAC + ICI
C57BL/6
C57BL/6
Optimal protection of TB granuloma
T_H1 (IFNγ)
T_H2 (Stat 6)
Epithelioid MP
TNF
IL-12
IL-17
MMPs
Hypoxia
IDO-1
HO-1
Aerobic glycolysis
HIF1α
ICI
LTA4H (CC)
Immune variable deficient
Immune variable excess
("DTH")